16.1.1 Protocol and Protocol Amendments

The latest version of the study protocol and all previous versions are provided on the following pages:

- V10.0, 12 Feb 2018 (per Amendment 04)
- V9.0, 12 Dec 2017 (per administrative corrections)
- V8.0, 12 Dec 2017 (per Amendment 03)
- v7.0, 11 Jul 2017 (per Amendment 02)
- v6.0, 17 May 2017 (per Amendment 01)
- v5.0. 22 Feb 2017 (Revision)
- v4.0, 03 Nov 2016 (Revision)
- v3.0, 14 Sep 2016 (Revision)
- v2.0, 22 Jul 2016 (Revision)
- v1.0, 16 Apr 2015 (original protocol)

Revision History

Previous Version (Revision): v9.0

Current Version (Revision): v10.0

Date of Revisions: 12 Feb 2018 (per Amendment 04)

Change	Rationale	Affected Protocol Section(s)
Revised rescreening requirement	To facilitate recruitment	Section 2, Synopsis-Study Design Section 9.1 Section 9.3
Revised measurements of fasting glucose to fasting plasma glucose	Document consistency	Section 2, Synopsis-Other Secondary Objectives Section 8.2 Section 9.7.1.1.2
Revised in-text reference to cardiovascular disease from Exclusion Criterion #3 to Exclusion Criterion #4	Document quality	Section 2, Synopsis-Assessments
Revised safety analyses text for consistency throughout document	Document quality	Section 2, Synopsis-Assessments
Revised DEXA assessment to specify only in a subset of subjects and addition of Z-score for assessment	Clarification	Section 2, Synopsis-Objectives Section 2, Synopsis-Assessments Section 9.7.1.8 Section 9.7.1.8.6 Section 8.2 Section 9.5.1.5
Revised ordering of numbering of Exclusion Criteria in body for consistency in document	Document quality	Section 9.3.2
Addition of footnote “e”in assessment table to clarify procedure; subsequent renumbering of successive criteria	Clarification	Table 2
Removal of “US” designation from unscheduled laboratory tests as additional assessments are indicated in the clinical judgment of the investigator	Clarification	Table 2 Table 3
Clarifications of blood sample volumes	Clarification	Table 3
Grammatical, typographical, stylistic, and formatting changes were also made	Document quality	Throughout the document

Revision History Previous Version (Revision): v8.0 Current Version (Revision): v9.0 Date of Revisions: 12 Dec 2017 (per administrative corrections)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised assignment of assessment table footnotes	Clarity	Table 2

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised secondary objectives to assess effects of glycemia to fasting glucose in subjects with Type 2 diabetes and those without Type 2 diabetes	Per FDA request	Synopsis – Objective Section 8.2 Section 9.7.1.1.2
Added secondary objective to assess the effects on body fat and lean mass compostion by DEXA in a subset of subjects at selected sites	Per FDA request	Synopsis – Objective Synopsis - Efficacy Assessment Synopsis – Other Safety Assessments Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.1.2 Table 2 Section 9.7.1.8.6
Revised secondary objective for cardiovascular risk factors associated with obesity to include blood pressure and heart rate		Synopsis – Objective Section 8.2
Revised secondary objective to evaluate bone density by DEXA in a subset of subjects at baseline and Week 52/EOT	Per FDA request	Synopsis – Objective Synopsis - Other Safety Assessment Section 8.2 Section 9.5.1.5 Section 9.5.1.5.10 Table 2 Section 9.7.1.6 Section 9.7.1.8.6
Added requirement to evaluate drug compliance (via pill count)	Per FDA request	Synopsis – Other Secondary Efficacy Endpoints Section 9.4.7 Section 9.7.1.1.2
Revised to specifiy that at least 20% of all study subjects enrolled are younger (12 to 13 year of age)	Per FDA request	Synopsis - Study Design Section 9.1

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Added requirement that 80% of randomized subject will have primary endpoint assessments	Per FDA request	Synopsos – Study Design Section 9.5.1.3
Revised to specify that study sites will be selected to ensure adequate representation of adolescents of ethnic and racial minorities	Per FDA request	Synopsis - Efficacy Assessments Section 9.7.1.8.6
Added requirement for Data Monitoring Committee	Per FDA request	Synopsis - Study Design Section 9.1
Added assessment of anthropometric measure (waist circumfereance)	Per FDA request	Synopsis – Efficacy Assessments Section 9.5.1.3 Section 9.5.1.5.7
Revised inclusion criteria (#1) to define population at baseline with regard to Type 2 diabetes diagnosis	To ensure PPSR requirements are met	Synopsis - Inclusion Criteria Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.3.1
Added exclusion criteria (#3) for subjects with Type 2 diabetes who are hypoglycemia unaware	To ensure PPSR requirements are met	Synopsis - Exclusion Criteria Section 9.3.2
Revised concomitant medication guidelines	To provide futher clarity	Synopsis – Concomitant Drug/Therapy Section 9.4.6
Revised instructions on height and body weight measurements	Per FDA request	Synopsis – Study Design Section 9.1 Section 9.5.1.3 Section 9.5.1.5.5
Added instructions for investigator to monitor specific list of AEs that have occurred since the last visit	Per FDA request	Section 9.5.1.5.1
Added requirement for report hypoglycemic events for the subjects with type 2 diabetes	Per PPSR requirements	Section 9.5.1.5.1
Revised requirements for AE monitoring	Per PPSR requirements	Section 9.5.1.5.1

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised list of events that should be considered SAEs and reported as important medical events	Per PPSR requirements	Section 9.5.1.5.2 Section 9.5.4.3.2
Added requirement for querying sites for all relevant information for subjects lost to follow-up	Per FDA request	Section 9.5.5
Added requirement to provide proper training to all study participants and their parent/guardian, in order to achieve optimal subject retention and prevent missing data	Per FDA request	Section 9.5.5
Revised assessment timepoints for Tanner Staging, Testosterone/Estradiol, TSH, fasting prolactic, echocardiogram, OC/PICP/Hydroxy-proline, ECG, and Hand X-rays	Per FDA requeset	Table 2
Revised Other Secondary Efficacy Analyses text MMRM		Section 9.7.1.6

Revision History Previous Version (Revision): v6.0 Current Version (Revision): v7.0 Date of Revisions: 11 Jul 2017 (per Amendment 02)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised statistical power from 90% to 80%	80% statistical power would provide sufficent sample size to detect weight loss effects and evaluate lorcaserin safety in the population selected.	Synopsis – Study Design Synopsis – Number of Subjects Synopsis – Sample Size Rationale Section 7.1.2 Section 9.1 Section 9.2 Section 9.3 Section 9.7.2
Revised Other Secondary Endpoints	To align with recently submitted PPSR	Synopsis – Other Secondary Efficacy Endpoints Section 9.7.1.1.2
Added clarification on timing of PK samples taken during an early discontinuation visit	Clarification	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Revised scale for measuring of cognition from Wide Range Assessment of Memory and Learning-2 (WRAML-2) to Leiter-3	Leiter-3 is selected to replace WRAML-2 for the evaluation of the change in cognition for the following reasons:Lack of availability of WRAML-2 in Spanish, Leiter-3's high scientific validity, non-verbal format to offer less biased assessment for subjects whose second language is English, easier and shorter administration and short test time reducing investigator burden, as well as increase probability of the subjects' retention in the study.	Synopsis – Objectives Synopsis – Other Safety Assessments Synopsis – Other Safety Analyses List of Abbreviations Section 8.2 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Added requirement that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS	To provide guidance that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.	Synopsis – Other Safety Assessments Section 9.5.1.5.10
Revised timing of initial C-SSRS from Baseline to Screening	Operational efficiencies	Table 2 Section 9.3.2 Section 9.5.1.5.10
Correct formatting of Synopsis, Other Secondary Objectives	Consistency	Synopsis – Objectives Section 8.2
Revised exclusion criteria for viral hepatitis (B or C) (#17) whereby active testing will not be performed	To clarify that the subjects will be excluded if they are known to have active hepatitis (B or C). Hepatitis (B or C) tests will not be conducted for the screening purpose.	Synopsis – Exclusion Criteria Section 9.3.2
Added footnotes regarding collection of PK samples at EOT and Early Discontinuation visits	To ensure appropriate timing of sampling relative to administration of last dose of study drug	Table 2
Added clarification for Unscheduled visits, such that they may be conducted at any time that additional assessments are clinically indicated in the judgment of the investigator.	Provide additional guidance to investigators	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Added clarification that prolactin testing should be fasting	Clarification	Table 2
Added requirement for pregnancy test and AM serum cortisol to Early Discontinuation Visit	Correction	Table 2 Table 3
Added requirement for lifestyle modification counseling Visit at Week 16	To ensure all visits are 4 weeks apart	Table 2
General alignment of text throughout	Clarity	Throughout

Revision History

Previous Version (Revision): v4.0

Current Version (Revision): v5.0

Date of Revisions: 22 Feb 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis - Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis - Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis - Study Protocol Title Synopsis - Design Synopsis - Inclusion Criteria Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Other Secondary Objectives Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.3.2 Section 9.5.1.5.10 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis - Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis - Other Secondary Objectives Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis - Other Secondary Objectives Synopsis - Efficacy Assessments Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Removed Appendix 3	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History

Previous Version (Revision): v2.0

Current Version (Revision): v3.0

Date of Revisions: 14 Sep 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis - Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Synopsis - Analysis Sets Synopsis - Pharmacodynamic Analyses Synopsis - Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Section 9.3.1
The secondary efficacy objective and endpoint were revised	To explore the predictability of 12-week responders for long-term sustainable weight loss effect	Synopsis - Secondary Efficacy Objectives Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis - Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis - Study Protocol Title Synopsis - Objectives Synopsis - Study Design Synopsis - Inclusion Criteria Synopsis - Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.10 Section 9.7.1.6 Section 9.7.1.8
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis - Efficacy Assessments Synopsis - Pharmacokinetic Assessments Synopsis - Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.1

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Change to primary and key secondary endpoints	Per FDA request	Synopsis - Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis - Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis - Exclusion Criteria Synopsis - Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision) v6.0 17 May 2017 (per Amendment 01) v7.0 11 Jul 2017 (per Amendment 02) V8.0 12 Dec 2017 (per Amendment 03) V9.0 12 Dec 2017 (per administrative corrections) V10.0 12 Feb 2018 (per Amendment 04)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

TBD

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from the first subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting plamsa glucose, hemoglobin A_{1c} (HbA1C), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) in subjects with Type 2 Diabetes Mellitus (T2DM) at baseline during 52 weeks of treatment (revised per Amendments 03 and 04)
  - Effects on fasting plasma glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without T2DM at baseline during 52 weeks of treatment (revised per Amendments 03 and 04)
  - Effects on body fat and lean mass composition by Dual-energy X-ray Absorptiometry (DEXA) in a

subset of subjects (selected prior to randomization at selected sites) during 52 weeks of treatment (revised per Amendment 03)

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition with the Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by Centers for Disease Control and Prevention (CDC) growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass, and total body lean mass using DEXA in a subset of subjects (selected prior to randomization at selected sites), valvular function, and pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developed to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling. (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study visit.

Subjects who screen fail can be re-screened only once. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendments 03 and 04)

Study sites will be selected to ensure adequate representation of adolescents of ethnic and racial minorities. (revised per Amendment 03)

Data Monitoring Committee (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established.

Number of Subjects

Approximately 500 subjects will be screened to provide 260 randomized subjects. (revised per Amendment 02)

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of

T2DM.

Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and confirmed:

- HbA1c ≥6.5%
- fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With T2DM who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

   In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Subjects with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those subjects with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
   - Left ventricular ejection fraction <45%
   - Intracardiac mass, tumor or thrombus
   - Evidence of congenital heart disease

- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder (ADHD), any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:

    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

    - selective serotonin reuptake inhibitors (SSRIs)
    - serotonin norepinephrine reuptake inhibitors (SNRIs)
    - tricyclic antidepressants (TCAs)
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - linezolid
    - dextromethorphan in any form (eg, OTC cold medicines)
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

    b) Others

    - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
    - oral steroids (topical and inhaled steroids are acceptable)
    - stimulant medications (eg, Ritalin®, Concerta®, biphetamine, and Dexedrine®)
    - benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), T2DM treated with oral antidiabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening

19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
27. Planned bariatric surgery during the study or prior bariatric surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are

prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.
- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more antihyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or pulumonary hypertension (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendment 03)

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction
- Waist circumference (revised per Amendment 03)
- Total body fat mass and total body lean mass will be determined centrally using DEXA in a subset of subjects (selected prior to randomization at selected sites) at baseline and Week 52/EOT (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and Homeostasis Model Assessment of Insulin Resistance (HOMA–IR) to assess cardiovascular and metabolic risk profiles from baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

Pharmacokinetic Assessments

Blood samples (approximately 4 mL each) for PK assessment will be collected at Weeks 12, 28, 36, and 52 for analysis of Population PK. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit, and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing), and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for for PK assessments will be collected. Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (fasting plasma glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such as

galactorrhea, changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed.

Other Safety Assessments

Effect on growth will be evaluated using the CDC growth chart and bone age determination by x-ray of the hand. Sexual maturation will be evaluated by assessing sex hormones and Tanner Staging.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognition will be assessed using the Leiter-3. (revised per Amendment 01)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of subjects (selected prior to randomization at selected sites). (revised per Amendment 03)

Echocardiographic assessments will be used to exclude subjects with US Food and Drug Administration (FDA)-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 4) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity. (revised per Amendments 03 and 04)

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from baseline to Week 52
- Association between change and percentage change in BMI from baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from baseline to Week 52 for subjects with T2DM at baseline (revised per Amendment 03)
- Change in fasting plasma glucose, fasting insulin, and HOMA-IR from baseline to Week 52 for subjects

with T2DM at baseline (revised per Amendments03 and 04)

- Change in fasting plamsa glucose, fasting insulin, and HOMA-IR from baseline to Week 52 for the subjects without T2DM at baseline (revised per Amendments 03 and 04)
- Change in BP (systolic and diastolic) and heart rate from baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subjects compliance rate at each visit by pill count during 52 week treatment (revised per Amendment 03)

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at

Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White) and age. Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of subjects achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment for serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, vital sign measurements, bone mineral density and content, total body fat mass and total body lean mass by DEXA, FDA-defined valvulopathy, and pulmonary hypertension assessed by echocardiograph will be summarized by treatment group using descriptive statistics or frequency count as appropriate.

No hypothesis testing will be performed for the safety assessment. (Revised per Amendment 04)

Other Safety Analyses

In addition, cognition will be evaluated by the Leiter-3, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendments 01 and 03)

Abbreviation	Term
ADA	American Diabetes Association
AE	adverse event
AS	aortic stenosis
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DEXA	Dual-energy X-ray Absorptiometry
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation	Term
IxRS	interactive voice or web response system
LDL	low density lipoprotein
Leiter-3	Leiter-3 International Performance Scale
LNH	low/normal/high
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OGTT	oral glucose tolerance test
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PH	pulmonary hypertension
PHQ-9	Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	acceleration time measured at right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T2DM	Type 2 Diabetes Mellitus
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values

Abbreviation	Term
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity has become a global epidemic, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the first time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects

(Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies may be used in the present study to help retain participants. These include a highly trained and competent site staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, sites may utilize fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters to further encourage subject retention. Furthermore, we may make home visits for primary efficacy assessments, as needed, to maximize data collection. By incorporating some of these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 Diabetes Mellitus (T2DM), demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the

studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of

variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 260 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat sibutramine, and liraglutide 3 mg) (FDA, 2003; Chanoine, et al., 2005; Berkowitz, et al, 2006; CT.gov NCT02918279) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007). (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

- To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo (revised per Amendment 01)
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting plasma glucose, hemoglobin A1c (HbA1c), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); glucose [mg/dL] × insulin [mU/L]/405) in subjects with T2DM at baseline during 52 weeks of treatment (revised per Amendments 03 and 04)
  - Effects on fasting plasma glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without T2DM at baseline during 52 weeks of treatment (revised per Amendments 03 and 04)
  - Effects on body fat and lean mass composition by Dual-energy X-ray Absorptiometry (DEXA) in a subset of subjects (selected prior to randomization at selected sites) during 52 weeks of treatment (revised per Amendment 03)
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate) during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition by Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by CDC growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass and total body lean mass by DEXA in a subset of subjects (selected prior to randomization at selected sites), valvular function, pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developed to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2). (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be rescreened only once. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendments 03 and 04)

Study sites will be selected to ensure adequate representation of adolescents of ethinic and racial minorities. (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established. (revised per Amendment 03)

9.1.1 Prerandomization Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief

description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed

to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 260 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg. (revised per Amendment 02)

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 500 subjects will be screened to ensure that 260 subjects will be randomized. (revised per Amendment 02)

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be rescreened only once and without repeating the screening echocardiogram for up to 90 days after the previous echocardiogram. All other screening assessments must be repeated when a subject is rescreened. Subjects that rescreen more than 90 days after the previous echocardiogram must repeat all screening assessments including the screening echocardiogram. (revised per Amendments 03 and 04)

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of T2DM.

   Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

   Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and then confirmed:
   - HbA1c ≥6.5%
   - fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With T2DM who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on screening echocardiography:

   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
     - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Subjects with a

RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those subjects with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder (ADHD), any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) depressive disorder, bipolar disorder, or schizophrenia
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:
    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
        - selective serotonin reuptake inhibitors (SSRIs)
        - serotonin norepinephrine reuptake inhibitors (SNRIs)
        - tricyclic antidepressants (TCAs)
        - bupropion
        - triptans
        - St. John's Wort
        - tryptophan
        - linezolid
        - dextromethorphan in any form (eg, OTC cold medicines)
        - lithium
        - tramadol
        - antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin®, Concerta®, biphetamine and Dexedrine®)
- benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), T2DM treated with oral antidiabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening
19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent

27. Planned bariatric surgery during the study or prior bariatic surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Investigators should do their best to bring all subject who discontinued early from the study in for the their primary endpoint collection regardless of the reason for ED. (revised per Amendment 01)

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL). For information on dosing on visits associated with PK sampling, see Section 9.5.1.4.1. (revised per Amendment 03)

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.

- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more antihyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. (revised per Amendment 01) If any of the above agents are clinically warranted, and subjects initiate any of these agents, Belviq XR should be discontinued but can be restarted on Belviq XR after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendments 03 and 04)

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Subjects will be asked to bring their study drug bottles to each visit. The CRAs will review treatment compliance during site visits and at the completion of the study. (revised per Amendment 03)

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol

- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur

at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 URINE DRUG SCREEN

A 30-mL urine sample will be collected at Screening, as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines). (revised per Amendment 01)

9.5.1.3 Efficacy Assessments

- Body weight and height: will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI. Body weight will be measured in the morning after at least 8 hours of fasting and voiding using a calibrated scale and standardized instructions for clothing (ie, a hospital gown). Weight will be measured to the nearest 0.1 kg. Height will be measured in triplicate utilizing a stadiometer with a standardized process (eg, subjects should not be wearing shoes). Height must be measured to the nearest 0.1 cm. BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction. (revised per Amendment 03)

- Waist circumference: will be determined by measurement taken with a tape measure positioned horizontally, parallel to the floor, at one finger width above the iliac crest. The subject should be standing erect with relaxed abdominal muscles. The tape measure should be snug but not compress the skin. The waist circumference should be taken to the nearest 1.0 cm, at the end of normal expiration. Three measurements will be taken and the average will be calculated. (revised per Amendment 03)
- Total body fat mass and total body lean mass: will be determined centrally using DEXA in a subset of subjects (selected prior to randomization at selected sites) at bBseline and Week 52/EOT. (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for Population PK analyses. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood

sample for PK assessment will be collected**.** Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Lorcaserin plasma exposure from PK analysis and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (fasting plasma glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed. (revised per Amendments 03 and 04)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of subjects (selected prior to randomization at selected sites). (revised per Amendment 03)

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present at pretreatment (baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

At each visit, the investigator should actively assess as to whether any of the following adverse events have occurred during the interval since the last visit:

- Serotonin syndrome and signs or symptoms of serotonergism
- Signs or symptoms of valvular heart disease or pulmonary hypertension, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur

- Impairments in attention and memory, and confusion, somnolence, and fatigue
- Psychiatric disorders
- Hypoglycemia in subjects with diabetes on concomitant antidiabetes medications (using ADA definitions)
- Priapism and hyperprolactinemia signs and symptoms should be recorded at each visit and whenever reported
- Hypersensitivity reactions

Any such events should be recorded as adverse events. Serotonin syndrome, valvular heart disease, pulmonary hypertension, and priapism should always be reported as serious adverse events (SAEs) (See Section 9.5.1.5.2 for a complete list of adverse events that should always be considered as Serious). (revised per Amendment 03)

Events of hypoglycemia in subjects with diabetes on concomitant antidiabetes medication should be captured as per Section 9.5.2. Severe symptomatic events of hypoglycemia should always be reported as an SAE as per Section 9.5.1.5.2. (revised per Amendment 03)

It is the responsibility of the investigator to review the results of the Leiter-3, C-SSRS, and PHQ-9 for all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.10 for a description of the C-SSRS). (revised per Amendment 01)

All AEs must be monitored until symptom resolution, or until the condition stabalizes. (revised per Amendment 03)

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
- Severe symptomatic hypoglycemia (revised per Amendment 03)

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in

the study. Laboratory testing should be conducted on an unscheduled basis if clinically indicated. (revised per Amendment 03)

Table 1 Clinical Laboratory Tests (revised per Amendments 01, 03, and 04)

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium, bicarbonate
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	AM serum Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects)
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other (revised per Amendments 01 and 04)	Albumin, calcium, globulin, fasting plasma glucose, HbA_{1c}, HDL cholesterol, fasting insulin, lactate dehydrogenase, LDL cholesterol, fasting lipid panel, phosphorus, total protein, total cholesterol, triglycerides, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained in triplicate to the nearest 0.1 cm as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.1.5.6 CDC GROWTH MEASUREMENTS

Investigators will calculate the height for age percentile and weight for age percentile utilizing the most recent CDC 95th Percentile Growth Chart and the height and weight measurements obtained, as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.7 WAIST CIRCUMFERENCE

Waist circumference (cm) measurements will be obtained in triplicate to the nearest 1.0 cm taken 3 times at each visit as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendments 01 and 03)

9.5.1.5.8 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

As part of the physical examination, a neuromuscular sign assessment for serotonin syndrome will be performed for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF. (revised per Amendment 01)

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will also be captured in the AE eCRF. (revised per Amendment 01)

9.5.1.5.9 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.10 OTHER SAFETY ASSESSMENTS

Leiter-3

The Leiter International Performance Scale–Third Edition (Leiter-3) is widely used non verbal measure of intelligence, memory, and attention in those between the ages of 3 and 75 years. The Attention/Memory Battery consists of 5 subtests: 2 measure nonverbal attention; 2 measure memory; and 1 measures cognitive interference (nonverbal Stroop test). These subtests are combined to produce a Memory and Processing Speed composite scores, normalized to a mean of 100 and standard deviation of 15. The Leiter-3 will be used to assess lorcaserin effects on cognition, specifically, attention and memory. In addition, signs and symptoms of cognition-related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF. (revised per Amendment 01)

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the subject's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at Baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. Qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and

certification process for administering the C-SSRS. It will be performed at Screening and at study visits as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

DEXA for the Assessment of Bone Mineral Density

Bone mineral density body composition determination by DEXA whole body composition, to include bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of subjects (selected prior to randomization at selected sites). A contracted vendor will provide all administration and project management services for DEXA scanning. This will include site and image data management services, as well as site training and certification. (revised per Amendment 03)

A mininum of 30 subjects ages 12-17 years (selected prior to randomization at selected sites) should have bone density evaluated with DEXA at baseline and week 52/EOT. (revised per Amendments 03 and 04)

Hand X-Ray

A hand x-ray for evaluation of any potential negative effect on bone age will be performed on the same hand at each visit as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of subjects will be using Tanner Staging by a trained clinician (Marshall, 1970). Subjects will be examined by the investigator as designated in the Schedules/Assessments (Table 2). (revised per Amendments 01 and 03)

Echocardiogram

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery systolic pressure will be estimated from the TR regurgitant jet velocity. (revised per Amendment 03)

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at every visit as specified in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02, 03, and 04)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[d]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging		X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X		X
Urinalysis	X	X	X	X		X		X			X	X		X
Urine drug and cotinine test	X													
Fasting plasma glucose, insulin, and HbA1c sampling	X	X				X		X			X			X
T4 and TSH	X	X						X			X			X
Testosterone, Estradiol[e]		X						X			X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02, 03, and 04)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (urine)	X	X	X	X	X	X	X	X	X	X	X	X		X
Fasting prolactin	X	X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X[f]		X[f]	X[f]		X[f,g]		X[h]	X[g]
AM serum cortisol		X									X			X
ECG		X						X			X	X		
Echocardiograph	X[i]							X			X			
DEXA[j]		X									X			
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Hand x-ray for bone age		X									X			X
C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Leiter-3		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02, 03, and 04)

Phase:	Prerandomization[a]	Randomization												
Period:	Screening	Treatment[b]										Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Standardized age-appropriate lifestyle modification counseling[k]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, SAE = serious adverse event; T4 = thyroxine, TSH = thyroid stimulating hormone, US = unscheduled.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits. (revised per Amendments 01 and 03)

c: Unscheduled visits may be conducted at any time that additional assessments are indicated in the clinical judgment of the investigator. Note that not all assessments listed under Unscheduled Visit need to be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs. At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendments 01 and 03)

d: Includes a neuromuscular assessment for serotonin syndrome, and signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) (revised per Amendments 01 and 03)

e: Testosterone will only be drawn in males, and estradiol will only be drawn in females. (revised per Amendment 04)

f: On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessments will be collected Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

g: PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug.

h: PK samples should only be collected if subject has experienced an SAE while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE.

i: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

j: Only subjects in selected sites will have this assessment done. (revised per Amendment 03)

k: Lifestyle modification counseling will also be performed at Weeks 3, 16, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Appendix 2.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes (revised per Amendments 01, 03, and 04)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), EOS or ED	5×8=40
T4, TSH	2.5	Screening: 1 Visits 2, 8, 11 (EOT), or ED	2.5×4=10
Testosterone, estradiol	0.5	Visits 2, 8, 11 (EOT)	0.5x3=1.5
AM serum cortisol	0.5	Visits 2, 11 (EOT), or ED	0.5x2=1
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or ED	8×3=24
Fasting Prolactin, FPG, fasting insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or ED	5×6=30
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or ED (2 samples each); Visit 9 (1 sample only)	4×7=28
Total			134.5

ED= early discontinuation from study, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, OC = osteocalcin, PD = pharmacodynamic, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
- Severe symptomatic hypoglycemia (revised per Amendment 03)

Subject-reported episodes of hypoglycemia or decreased blood sugar should be captured on the eCRF according to the following guidelines:

- Pseudo-hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level. (revised per Amendment 03)
- Probable symptomatic hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)
- Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)

- Documented symptomatic hypoglycemia: An event during which typical hypoglycemia symptoms are accompanied by a measured plasma glucose ≤70 mg/dL (≤3.9 mmol/L) (revised per Amendment 03)
- Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitation actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (revised per Amendment 03)

See Section 9.4.6 (Prior and Concomitant Therapy) for directions on the recommendations for possible adjustment to antihyperglycemic medication doses in response to reported episodes of hypoglycemia. (revised per Amendment 03)

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue study drug prematurely will continue to be evaluated for all study assessments until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on IP at the end of the study. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments Table 2). (revised per Amendment 03)

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be contacted by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of the secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF. If "lost to follow-up" is recorded in clinical database, appropriate queries will be sent to investigators in order to collect all the relevant reasons for missing data. (revised per Amendment 03)

Every effort, including proper training of all study participants and their parent/guardian, should be made in order to achieve optimal subject retention and prevent missing data, especially for the Week 52 primary endpoint. A retention plan to help avoid missing data will be developed and included in study manual. (revised per Amendment 03)

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from baseline to Week 52
- Association between change and percentage change in BMI from baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from baseline to Week 52 for subjects with T2DM at baseline (revised per Amendment 03)
- Change in fasting plasma glucose, fasting insulin, and HOMA-IR from baseline to Week 52 for subjects with T2DM at baseline (revised per Amendments 03 and 04)
- Change in fasting plasma glucose, fasting insulin, and HOMA-IR from baseline to Week 52 for the subjects without T2DM at baseline (revised per Amendments 03 and 04)
- Change in BP (systolic and diastolic) and heart rate from baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subject compliance rate at each visit by pill count during 52 weeks of treatement (per Amendment 03)

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant

medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) on the FAS for study treatment compared to placebo, as appropriate. The model will include all data and will include treatment, time, and the interaction of treatment by time as fixed effects, with adjustment for sex (male versus female), BMI and age at baseline, and subject as a random effect. (revised per Amendment 03)

Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The MMRM model assumes that the missing data are missing at random and makes use of all available data even if a subject has missing data at some postbaseline visits. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. (revised per Amendment 03)

Categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White), and age. Additional subgroups may be explored, if deemed necessary. (revised per Amendment 03)

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual

posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of subjects achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment for serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, vital sign measurements, bone mineral density and content, total body fat mass and total body lean mass by DEXA, FDA-defined valvulopathy, and pulmonary hypertension by echocardiograph will be summarized by treatment group using descriptive statistics or frequency count as appropriate. (revised per Amendments 01, 03, and 04)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the first dose of study drug and the date the subject received the last dose of study

drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value

and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and

- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, study drug effect on cognition assessed by Leiter-3, assessment of suicidality using C-SSRS, depression assessment using PHQ-9, will be summarized by treatment group at each scheduled visit. In a subset of subjects, bone mineral density and content, total body fat mass, and total body lean mass using DEXA and their z-score will be summarized by treatment group at baseline and Week 52. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52. (revised per Amendments 01, 03, and 04)

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number: APD356-A001-403

Study Protocol Title: A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigational Product Name: APD356/Belviq XR® (lorcaserin hydrochloride)

IND Number: 069888

SIGNATURES

Authors:

PPD

Neurology Business Group
Eisai Inc.

Date

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Medicine Development Group
Eisai Inc.

Date

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Neurology Business Group
Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Revision): v8.0 Current Version (Revision): v9.0 Date of Revisions: 12 Dec 2017 (per administrative corrections)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised assignment of assessment table footnotes	Clarity	Table 2

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised secondary objectives to assess effects of glycemia to fasting glucose in subjects with Type 2 diabetes and those without Type 2 diabetes	Per FDA request	Synopsis – Objective Section 8.2 Section 9.7.1.1.2
Added secondary objective to assess the effects on body fat and lean mass compostion by DEXA in a subset of subjects at selected sites	Per FDA request	Synopsis – Objective Synopsis - Efficacy Assessment Synopsis – Other Safety Assessments Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.1.2 Table 2 Section 9.7.1.8.6
Revised secondary objective for cardiovascular risk factors associated with obesity to include blood pressure and heart rate		Synopsis – Objective Section 8.2
Revised secondary objective to evaluate bone density by DEXA in a subset of subjects at baseline and Week 52/EOT	Per FDA request	Synopsis – Objective Synopsis - Other Safety Assessment Section 8.2 Section 9.5.1.5 Section 9.5.1.5.10 Table 2 Section 9.7.1.6 Section 9.7.1.8.6
Added requirement to evaluate drug compliance (via pill count)	Per FDA request	Synopsis – Other Secondary Efficacy Endpoints Section 9.4.7 Section 9.7.1.1.2
Revised to specifiy that at least 20% of all study subjects enrolled are younger (12 to 13 year of age)	Per FDA request	Synopsis - Study Design Section 9.1

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Added requirement that 80% of randomized subject will have primary endpoint assessments	Per FDA request	Synopsos – Study Design Section 9.5.1.3
Revised to specify that study sites will be selected to ensure adequsate representation of adolescents of ethnic and racial minorities	Per FDA request	Synopsis - Efficacy Assessments Section 9.7.1.8.6
Added requirement for Data Monitoring Committee	Per FDA request	Synopsis - Study Design Section 9.1
Added assessment of anthropometric measure (waist circumfereance)	Per FDA request	Synopsis – Efficacy Assessments Section 9.5.1.3 Section 9.5.1.5.7
Revised inclusion criteria (#1) to define population at baseline with regard to Type 2 diabetes diagnosis	To ensure PPSR requirements are met	Synopsis - Inclusion Criteria Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.3.1
Added exclusion criteria (#3) for subjects with Type 2 diabetes who are hypoglycemia unaware	To ensure PPSR requirements are met	Synopsis - Exclusion Criteria Section 9.3.2
Revised concomitant medication guidelines	To provide futher clarity	Synopsis – Concomitant Drug/Therapy Section 9.4.6
Revised instructions on height and body weight measurements	Per FDA request	Synopsis – Study Design Section 9.1 Section 9.5.1.3 Section 9.5.1.5.5
Added instructions for investigator to monitor specific list of AEs that have occurred since the last visit	Per FDA request	Section 9.5.1.5.1
Added requiirement for report hypoglycemic events for the subjects with type 2 diabetes	Per PPSR requirements	Section 9.5.1.5.1
Revised requirements for AE monitoring	Per PPSR requirements	Section 9.5.1.5.1

Revision History Previous Version (Revision): v7.0 Current Version (Revision): v8.0 Date of Revisions: 12 Dec 2017 (per Amendment 03)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised list of events that should be considered SAEs and reported as important medical events	Per PPSR requirements	Section 9.5.1.5.2 Section 9.5.4.3.2
Added requirement for querying sites for all relevant information for subjects lost to follow-up	Per FDA request	Section 9.5.5
Added requirement to provide proper training to all study participants and their parent/guardian, in order to achieve optimal subject retention and prevent missing data	Per FDA request	Section 9.5.5
Revised assessment timepoints for Tanner Staging, Testosterone/Estradiol, TSH, fasting prolactic, echocardiogram, OC/PICP/Hydroxy-proline, ECG, and Hand X-rays	Per FDA requeset	Table 2
Revised Other Secondary Efficacy Analyses text MMRM		Section 9.7.1.6

Revision History Previous Version (Revision): v6.0 Current Version (Revision): v7.0 Date of Revisions: 11 Jul 2017 (per Amendment 02)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised statistical power from 90% to 80%	80% statistical power would provide sufficent sample size to detect weight loss effects and evaluate lorcaserin safety in the population selected.	Synopsis – Study Design Synopsis – Number of Subjects Synopsis – Sample Size Rationale Section 7.1.2 Section 9.1 Section 9.2 Section 9.3 Section 9.7.2
Revised Other Secondary Endpoints	To align with recently submitted PPSR	Synopsis – Other Secondary Efficacy Endpoints Section 9.7.1.1.2
Added clarification on timing of PK samples taken during an early discontinuation visit	Clarification	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Revised scale for measuring of cognition from Wide Range Assessment of Memory and Learning-2 (WRAML-2) to Leiter-3	Leiter-3 is selected to replace WRAML-2 for the evaluation of the change in cognition for the following reasons:Lack of availability of WRAML-2 in Spanish, Leiter-3's high scientific validity, non-verbal format to offer less biased assessment for subjects whose second language is English, easier and shorter administration and short test time reducing investigator burden, as well as increase probability of the subjects' retention in the study.	Synopsis – Objectives Synopsis – Other Safety Assessments Synopsis – Other Safety Analyses List of Abbreviations Section 8.2 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Added requirement that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS	To provide guidance that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.	Synopsis – Other Safety Assessments Section 9.5.1.5.10
Revised timing of initial C-SSRS from Baseline to Screening	Operational efficiencies	Table 2 Section 9.3.2 Section 9.5.1.5.10
Correct formatting of Synopsis, Other Secondary Objectives	Consistency	Synopsis – Objectives Section 8.2
Revised exclusion criteria for viral hepatitis (B or C) (#17) whereby active testing will not be performed	To clarify that the subjects will be excluded if they are known to have active hepatitis (B or C). Hepatitis (B or C) tests will not be conducted for the screening purpose.	Synopsis – Exclusion Criteria Section 9.3.2
Added footnotes regarding collection of PK samples at EOT and Early Discontinuation visits	To ensure appropriate timing of sampling relative to administration of last dose of study drug	Table 2
Added clarification for Unscheduled visits, such that they may be conducted at any time that additional assessments are clinically indicated in the judgment of the investigator.	Provide additional guidance to investigators	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Added clarification that prolactin testing should be fasting	Clarification	Table 2
Added requirement for pregnancy test and AM serum cortisol to Early Discontinuation Visit	Correction	Table 2 Table 3
Added requirement for lifestyle modification counseling Visit at Week 16	To ensure all visits are 4 weeks apart	Table 2
General alignment of text throughout	Clarity	Throughout

Revision History

Previous Version (Revision): v4.0

Current Version (Revision): v5.0

Date of Revisions: 22 Feb 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis - Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis - Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis - Study Protocol Title Synopsis - Design Synopsis - Inclusion Criteria Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Other Secondary Objectives Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.3.2 Section 9.5.1.5.10 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis - Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis - Other Secondary Objectives Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis - Other Secondary Objectives Synopsis - Efficacy Assessments Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Removed Appendix 3	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History

Previous Version (Revision): v2.0

Current Version (Revision): v3.0

Date of Revisions: 14 Sep 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis - Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Synopsis - Analysis Sets Synopsis - Pharmacodynamic Analyses Synopsis - Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Section 9.3.1
The secondary efficacy objective and endpoint were revised	To explore the predictability of 12-week responders for long-term sustainable weight loss effect	Synopsis - Secondary Efficacy Objectives Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis - Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis - Study Protocol Title Synopsis - Objectives Synopsis - Study Design Synopsis - Inclusion Criteria Synopsis - Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.10 Section 9.7.1.6 Section 9.7.1.8
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis - Efficacy Assessments Synopsis - Pharmacokinetic Assessments Synopsis - Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.1

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Change to primary and key secondary endpoints	Per FDA request	Synopsis - Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis - Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis - Exclusion Criteria Synopsis - Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision) v6.0 17 May 2017 (per Amendment 01) v7.0 11 Jul 2017 (per Amendment 02) V8.0 12 Dec 2017 (per Amendment 03) V9.0 12 Dec 2017 (per administrative corrections)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

TBD

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting glucose, hemoglobin A_{1c} (HbA1C), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) in subjects with Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on fasting glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on body fat and lean mass composition by Dual-enerygy X-ray Absorptiometry (DEXA) in a subset of randomized subjects (selected prio to randomization) at selected sites during 52 weeks of

treatment (revised per Amendment 03)

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition with the Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by Centers for Disease Control and Prevention (CDC) growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass, and total body lean mass using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites, valvular function, and pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developed to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling. (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 30 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendment 03)

Study sites will be selected to ensure adequate representation of adolescents of ethnic and racial minorities. (revised per Amendment 03)

Data Monitoring Committee (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established.

Number of Subjects

Approximately 500 subjects will be screened to provide 260 randomized subjects. (revised per Amendment 02)

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of

T2DM.

Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and confirmed:

- HbA1c ≥6.5%
- fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With Type 2 diabetes who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

   In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
   - Left ventricular ejection fraction <45%
   - Intracardiac mass, tumor or thrombus
   - Evidence of congenital heart disease

- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:

    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

    - selective serotonin reuptake inhibitors (SSRIs)
    - serotonin norepinephrine reuptake inhibitors (SNRIs)
    - tricyclic antidepressants (TCAs)
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - linezolid
    - dextromethorphan in any form (eg, OTC cold medicines)
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

    b) Others

    - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
    - oral steroids (topical and inhaled steroids are acceptable)
    - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
    - benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening

19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
27. Planned bariatric surgery during the study or prior bariatric surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are

prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.
- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more anti-hyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or pulumonary hypertension (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendment 03)

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction.
- Waist circumference (revised per Amendment 03)
- Total body fat mass and total body lean mass will be determined centrally using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites at Baseline and Week 52/EOT (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

Pharmacokinetic Assessments

Blood samples (approximately 4 mL each) for PK assessment will be collected at Weeks 12, 28, 36, and 52 for analysis of Population PK. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit,but to bring their study drug to the clinic visit, and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing), and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for for PK assessments will be collected. Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (fasting glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea,

changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed.

Other Safety Assessments

Effect on growth will be evaluated using the CDC growth chart and bone age determination by x-ray of the hand. Sexual maturation will be evaluated by assessing sex hormones and Tanner Staging.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognition will be assessed using the Leiter-3. (revised per Amendment 01)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites. (revised per Amendment 03)

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed only for subjects at selected sites. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity. (revised per Amendment 03)

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from Baseline to Week 52 for subjects with Type 2 diabetes as baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for subjects with

Type 2 diabetes as baseline (revised per Amendment 03)

- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for the subjects without Type 2 diabetes at baseline (revised per Amendment 03)
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subjects compliance rate at each visit by pill count during 52 week treatment (revised per Amendment 03)

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at

Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White) and age. Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate.

Other Safety Analyses

In addition, cognition will be evaluated by the Leiter-3, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary

hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendments 01 and 03)

Abbreviation	Term
ADA	American Diabetes Association
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DEXA	Dual-energy X-ray Absorptiometry
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
Leiter-3	Leiter-3 International Performance Scale

Abbreviation	Term
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OGTT	oral glucose tolerance test
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PH	pulmonary hypertension
PHQ-9	Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal

Abbreviation	Term
US	United States
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity has become a global epidemic, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects

(Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies may be used in the present study to help retain participants. These include a highly trained and competent site staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, sites may utilize fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters to further encourage subject retention. Furthermore, we may make home visits for primary efficacy assessments, as needed, to maximize data collection. By incorporating some of these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the

studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of

variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 260 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat sibutramine, and liraglutide 3 mg) (FDA, 2003; Chanoine, et al., 2005; Berkowitz, et al, 2006; CT.gov NCT02918279) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007). (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

- To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo (revised per Amendment 01)
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting glucose, hemoglobin A1c (HbA1c), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) in subjects with Type 2 diabetes at baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on fasting glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on body fat and lean mass composition by Dual-enerygy X-ray Absorptiometry (DEXA) in a subset of randomized subjects (selected prior to randomization) at selected sites during 52 weeks of treatment (revised per Amendment 03)
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate) during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition by Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by CDC growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass and total body lean mass by DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites, valvular function, pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developled to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2). (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be rescreened only once after 30 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendment 03)

Study sites will be selected to ensure adequate representation of adolescents of ethinic and racial minorities. (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established. (revised per Amendment 03)

9.1.1 Prerandomization Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief

description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed

to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 260 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg. (revised per Amendment 02)

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 500 subjects will be screened to ensure that 260 subjects will be randomized. (revised per Amendment 02)

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened immediately without repeating the screening echocardiogram for up to 90 days after the previous echocardiogram. All other screening assessments must be repeated when a subject is re-screened. Subjects that re-screen more than 90 days after the previous echocardiogram must repeat all screening assessments including the screening echocardiogram. (revised per Amendment 03)

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of T2DM.

   Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

   Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and then confirmed:
   - HbA1c ≥6.5%
   - fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With Type 2 diabetes who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on screening echocardiography:

   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
     - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a

RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, bipolar disorder, or schizophrenia
7. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
8. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:
    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
        - selective serotonin reuptake inhibitors (SSRIs)
        - serotonin norepinephrine reuptake inhibitors (SNRIs)
        - tricyclic antidepressants (TCAs)
        - bupropion
        - triptans
        - St. John's Wort
        - tryptophan
        - linezolid
        - dextromethorphan in any form (eg, OTC cold medicines)
        - lithium
        - tramadol
        - antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening
19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent

27. Planned bariatric surgery during the study or prior bariatic surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Investigators should do their best to bring all subject who discontinued early from the study in for the their primary endpoint collection regardless of the reason for ED. (revised per Amendment 01)

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL). For information on dosing on visits associated with PK sampling, see Section 9.5.1.4.1. (revised per Amendment 03)

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.

- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more anti-hyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. (revised per Amendment 01) If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendment 03)

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Subjects will be asked to bring their study drug bottles to each visit. The CRAs will review treatment compliance during site visits and at the completion of the study. (revised per Amendment 03)

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol

- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur

at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 URINE DRUG SCREEN

A 30-mL urine sample will be collected at Screening, as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines). (revised per Amendment 01)

9.5.1.3 Efficacy Assessments

- Body weight and height: will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI. Body weight will be measured in the morning after at least 8 hours of fasting and voiding using a calibrated scale and standardized instructions for clothing (ie, a hospital gown). Weight will be measured to the nearest 0.1 kg. Height will be measured in triplicate utilizing a stadiometer with a standardized process (eg, subjects should not be wearing shoes). Height must be measured to the nearest 0.1 cm. BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction. (revised per Amendment 03)

- Waist circumference: will be determined by measurement taken with a tape measure positioned horizontally, parallel to the floor, at one finger width above the iliac crest. The subject should be standing erect with relaxed abdominal muscles. The tape measure should be snug but not compress the skin. The waist circumference should be taken to the nearest 1.0 cm, at the end of normal expiration. Three measurements will be taken and the average will be calculated. (revised per Amendment 03)
- Total body fat mass and total body lean mass: will be determined centrally using DEXA in a subset of randomized subjects (selected prior to randomization at selected sites) at Baseline and Week 52/EOT. (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for Population PK analyses. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood

sample for PK assessment will be collected**.** Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Lorcaserin plasma exposure from PK analysis and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (fasting glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed. (revised per Amendment 03)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites. (revised per Amendment 03)

9.5.1.5.1 **ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

At each visit, the investigator should actively assess as to whether any of the following adverse events have occurred during the interval since the last visit:

- Serotonin syndrome and signs or symptoms of serotonergism
- Signs or symptoms of valvular heart disease or pulmonary hypertension, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur

- Impairments in attention and memory, and confusion, somnolence, and fatigue
- Psychiatric disorders
- Hypoglycemia in subjects with diabetes on concomitant anti-diabetes medications (using ADA definitions)
- Priapism and hyperprolactinemia signs and symptoms should be recorded at each visit and whenever reported
- Hypersensitivity reactions

Any such events should be recorded as adverse events. Serotonin syndrome, valvular heart disease, pulmonary hypertension, and priapism should always be reported as serious adverse events (SAEs) (See Section 9.5.1.5.2 for a complete list of adverse events that should always be considered as Serious). (revised per Amendment 03)

Events of hypoglycemia in subjects with diabetes on concomitant anti-diabetes medication should be captured as per Section 9.5.2. Severe symptomatic events of hypoglycemia should always be reported as an SAE as per Section 9.5.1.5.2. (revised per Amendment 03)

It is the responsibility of the investigator to review the results of the Leiter-3, C-SSRS, and PHQ-9 for all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.10 for a description of the C-SSRS). (revised per Amendment 01)

All AEs must be monitored until symptom resolution, or until the condition stabalizes. (revised per Amendment 03)

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
- Severe symptomatic hypoglycemia (revised per Amendment 03)

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in

the study. Laboratory testing should be conducted on an unscheduled basis if clinically indicated. (revised per Amendment 03)

Table 1 Clinical Laboratory Tests (revised per Amendments 01 and 03)

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium, bicarbonate
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	AM serum Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects)
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other (revised per Amendment 01)	Albumin, calcium, globulin, fasting glucose, HbA_{1c}, HDL cholesterol, fasting insulin, lactate dehydrogenase, LDL cholesterol, fasting lipid panel, phosphorus, total protein, total cholesterol, triglycerides,, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained in triplicate to the nearest 0.1 cm as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.1.5.6 CDC GROWTH MEASUREMENTS

Investigators will calculate the height for age percentile and weight for age percentile utilizing the most recent CDC 95th Percentile Growth Chart and the height and weight measurements obtained, as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.7 WAIST CIRCUMFERENCE

Waist circumference (cm) measurements will be obtained in triplicate to the nearest 1.0 cm taken 3 times at each visit as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendments 01 and 03)

9.5.1.5.8 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

As part of the physical examination, a neuromuscular sign assessment for serotonin syndrome will be performed for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF. (revised per Amendment 01)

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will also be captured in the AE eCRF. (revised per Amendment 01)

9.5.1.5.9 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.10 OTHER SAFETY ASSESSMENTS

Leiter-3

The Leiter International Performance Scale–Third Edition (Leiter-3) is widely used non verbal measure of intelligence, memory, and attention in those between the ages of 3 and 75 years. The Attention/Memory Battery consists of 5 subtests: 2 measure nonverbal attention; 2 measure memory; and 1 measures cognitive interference (nonverbal Stroop test). These subtests are combined to produce a Memory and Processing Speed composite scores, normalized to a mean of 100 and standard deviation of 15. The Leiter-3 will be used to assess lorcaserin effects on cognition, specifically, attention and memory. In addition, signs and symptoms of cognition-related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF. (revised per Amendment 01)

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. Qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and

certification process for administering the C-SSRS. It will be performed at Screening and at study visits as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

DEXA for the Assessment of Bone Mineral Density

Bone mineral density body composition determination by DEXA whole body composition, to include bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset subjects (selected prior to randomization) at selected sites. A contracted vendor will provide all administration and project management services for DEXA scanning. This will include site and image data management services, as well as site training and certification. (revised per Amendment 03)

A miminum of 30 subjects ages 12-18 years (selected prior to randomization) should have bone density evaluated with DEXA at BL and week 52/EOT. (revised per Amendment 03)

Hand X-Ray

A hand x-ray for evaluation of any potential negative effect on bone age will be performed on the same hand at each visit as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of subjects will be using Tanner Staging by a trained clinician (Marshall, 1970). Subjects will be examined by the investigator as designated in the Schedules/Assessments (Table 2). (revised per Amendments 01 and 03)

Echocardiogram

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery systolic pressure will be estimated from the TR regurgitant jet velocity. (revised per Amendment 03)

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at every visit as specified in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[d]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging		X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X	X	X	X		X		X			X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, insulin, and HbA1c sampling	X	X				X		X			X			X
T4 and TSH	X	X						X			X			X
Testosterone, Estradiol		X						X			X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (urine)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting prolactin	X	X				X		X			X		X	X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X[e]		X[e]	X[e]		X[e,f]		X[g]	X[f]
AM serum cortisol		X									X			X
ECG		X						X			X	X		
Echocardiograph	X[h]							X			X			
DEXA[i]		X									X			
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Hand x-ray for bone age		X									X			X
C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Leiter-3		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	Prerandomization[a]	Randomization												
Period:	Screening	Treatment[b]										Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Standardized age-appropriate lifestyle modification counseling[j]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, SAE = serious adverse event; T4 = thyroxine, TSH = thyroid stimulating hormone, US = unscheduled.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits. (revised per Amendments 01 and 03)

c: Unscheduled visits may be conducted at any time that additional assessments are indicated in the clinical judgment of the investigator. Note that not all assessments listed under Unscheduled Visit need to be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs. At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendments 01 and 03)

d: Includes a neuromuscular assessment for serotonin syndrome, and signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) (revised per Amendments 01 and 03)

e: On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessments will be collected Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

f: PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug.

g: PK samples should only be collected if subject has experienced an SAE while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE.

h: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

i: Only subjects in selected sites will have this assessment done. (revised per Amendment 03)

j: Lifestyle modification counseling will also be performed at Weeks 3, 16, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Appendix 2.

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9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes (revised per Amendments 01 and 03)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), EOS or ED	5×8=40
T4, TSH, AM Serum Cortisol, Testosterone, estradiol	6	Screening: 1 Visits 2, 8, 11 (EOT), or ED	6×4=24
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or ED	8×3=24
Fasting Prolactin, FPG, fasting insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or ED, US	5×6=30
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or ED (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			146

ED= early discontinuation from study, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, OC = osteocalcin, PD = pharmacodynamic, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious

criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
-
- Severe symptomatic hypoglycemia (revised per Amendment 03)

Subject-reported episodes of hypoglycemia or decreased blood sugar should be captured on the eCRF according to the following guidelines:

- Psuedo-hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level. (revised per Amendment 03)
- Probable symptomatic hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)
- Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)
- Documented symptomatic hypoglycemia: An event during which typical hypoglycemia symptoms are accompanied by a measured plasma glucose ≤70 mg/dL (≤3.9 mmol/L) (revised per Amendment 03)

- Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitation actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (revised per Amendment 03)

See Section 9.4.6 (Prior and Concomitant Therapy) for directions on the recommendations for possible adjustment to antihyperglycemic medication doses in response to reported episodes of hypoglycemia. (revised per Amendment 03)

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue study drug prematurely will continue to be evaluated on for all study assessments until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on IP at the end of the study. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments Table 2). (revised per Amendment 03)

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be contacted by

mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of the secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF. If "lost to follow-up" is recorded in clinical data base, appropriate queries will be sent to investigators in order to collect all the relevant reasons for missing data. (revised per Amendment 03)

Every effort, including proper training of all study participants and their parent/guardian, should be made in order to achieve optimal subject retention and prevent missing data, especially for the Week 52 primary endpoint. A retention plan to help avoid missing data will be developed and included in study manual. (revised per Amendment 03)

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH

guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12

- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from Baseline to Week 52 for subjects with Type 2 diabetes at baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for subjects with Type 2 diabetes at baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for the subjects without Type 2 diabetes at baseline (revised per Amendment 03)
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subject compliance rate at each visit by pill count during 52 weeks of treatement (per Amendment 03)

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) on the FAS for study treatment compared to placebo, as appropriate. The model will include all data and will include treatment, time, and the interaction of treatment by time as fixed effects, with adjustment for sex (male versus female), BMI and age at baseline, and subject as a random effect. (revised per Amendment 03)

Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The MMRM model assumes that the missing data are missing at random and

makes use of all available data even if a subject has missing data at some post-baseline visits. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. (revised per Amendment 03)

Categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White), and age. Additional subgroups may be explored, if deemed necessary. (revised per Amendment 03)

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment for serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, vital sign measurements, bone mineral density and content, total body fat mass and total body lean mass will be summarized by treatment group using descriptive statistics or frequency count as appropriate. (revised per Amendments 01 and 03)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also

compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, study drug effect on cognition assessed by Leiter-3, assessment of suicidality using C-SSRS, depression assessment using PHQ-9, bone mineral density and content, total body fat mass, and total body lean mass using DEXA will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by

echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52. (revised per Amendments 01 and 03)

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number: APD356-A001-403

Study Protocol Title: A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigational Product Name: APD356/Belviq XR® (lorcaserin hydrochloride)

IND Number: 069888

SIGNATURES

Authors:

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Eisai Inc.

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PPD Medicine Development Group
Eisai Inc.

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Date

Neurology Business Group
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised secondary objectives to assess effects of glycemia to fasting glucose in subjects with Type 2 diabetes and those without Type 2 diabetes	Per FDA request	Synopsis – Objective Section 8.2 Section 9.7.1.1.2
Added secondary objective to assess the effects on body fat and lean mass compostion by DEXA in a subset of subjects at selected sites	Per FDA request	Synopsis – Objective Synopsis - Efficacy Assessment Synopsis – Other Safety Assessments Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.1.2 Table 2 Section 9.7.1.8.6
Revised secondary objective for cardiovascular risk factors associated with obesity to include blood pressure and heart rate		Synopsis – Objective Section 8.2
Revised secondary objective to evaluate bone density by DEXA in a subset of subjects at baseline and Week 52/EOT	Per FDA request	Synopsis – Objective Synopsis - Other Safety Assessment Section 8.2 Section 9.5.1.5 Section 9.5.1.5.10 Table 2 Section 9.7.1.6 Section 9.7.1.8.6
Added requirement to evaluate drug compliance (via pill count)	Per FDA request	Synopsis – Other Secondary Efficacy Endpoints Section 9.4.7 Section 9.7.1.1.2
Revised to specifiy that at least 20% of all study subjects enrolled are younger (12 to 13 year of age)	Per FDA request	Synopsis - Study Design Section 9.1

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Added requirement that 80% of randomized subject will have primary endpoint assessments	Per FDA request	Synopsos – Study Design Section 9.5.1.3
Revised to specify that study sites will be selected to ensure adequsate representation of adolescents of ethnic and racial minorities	Per FDA request	Synopsis - Efficacy Assessments Section 9.7.1.8.6
Added requirement for Data Monitoring Committee	Per FDA request	Synopsis - Study Design Section 9.1
Added assessment of anthropometric measure (waist circumfereance)	Per FDA request	Synopsis – Efficacy Assessments Section 9.5.1.3 Section 9.5.1.5.7
Revised inclusion criteria (#1) to define population at baseline with regard to Type 2 diabetes diagnosis	To ensure PPSR requirements are met	Synopsis - Inclusion Criteria Synopsis – Other Secondary Efficacy Endpoints Section 8.2 Section 9.3.1
Added exclusion criteria (#3) for subjects with Type 2 diabetes who are hypoglycemia unaware	To ensure PPSR requirements are met	Synopsis - Exclusion Criteria Section 9.3.2
Revised concomitant medication guidelines	To provide futher clarity	Synopsis – Concomitant Drug/Therapy Section 9.4.6
Revised instructions on height and body weight measurements	Per FDA request	Synopsis – Study Design Section 9.1 Section 9.5.1.3 Section 9.5.1.5.5
Added instructions for investigator to monitor specific list of AEs that have occurred since the last visit	Per FDA request	Section 9.5.1.5.1
Added requiirement for report hypoglycemic events for the subjects with type 2 diabetes	Per PPSR requirements	Section 9.5.1.5.1
Revised requirements for AE monitoring	Per PPSR requirements	Section 9.5.1.5.1

Revision History

Previous Version (Revision): v7.0

Current Version (Revision): v8.0

Date of Revisions: 12 Dec 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised list of events that should be considered SAEs and reported as important medical events	Per PPSR requirements	Section 9.5.1.5.2 Section 9.5.4.3.2
Added requirement for querying sites for all relevant information for subjects lost to follow-up	Per FDA request	Section 9.5.5
Added requirement to provide proper training to all study participants and their parent/guardian, in order to achieve optimal subject retention and prevent missing data	Per FDA request	Section 9.5.5
Revised assessment timepoints for Tanner Staging, Testosterone/Estradiol, TSH, fasting prolactic, echocardiogram, OC/PICP/Hydroxy-proline, ECG, and Hand X-rays	Per FDA requeset	Table 2
Revised Other Secondary Efficacy Analyses text MMRM		Section 9.7.1.6

Revision History

Previous Version (Revision): v6.0

Current Version (Revision): v7.0

Date of Revisions: 11 Jul 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Section(s)
Revised statistical power from 90% to 80%	80% statistical power would provide sufficent sample size to detect weight loss effects and evaluate lorcaserin safety in the population selected.	Synopsis – Study Design Synopsis – Number of Subjects Synopsis – Sample Size Rationale Section 7.1.2 Section 9.1 Section 9.2 Section 9.3 Section 9.7.2
Revised Other Secondary Endpoints	To align with recently submitted PPSR	Synopsis – Other Secondary Efficacy Endpoints Section 9.7.1.1.2
Added clarification on timing of PK samples taken during an early discontinuation visit	Clarification	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Revised scale for measuring of cognition from Wide Range Assessment of Memory and Learning-2 (WRAML-2) to Leiter-3	Leiter-3 is selected to replace WRAML-2 for the evaluation of the change in cognition for the following reasons:Lack of availability of WRAML-2 in Spanish, Leiter-3's high scientific validity, non-verbal format to offer less biased assessment for subjects whose second language is English, easier and shorter administration and short test time reducing investigator burden, as well as increase probability of the subjects' retention in the study.	Synopsis – Objectives Synopsis – Other Safety Assessments Synopsis – Other Safety Analyses List of Abbreviations Section 8.2 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Added requirement that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS	To provide guidance that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.	Synopsis – Other Safety Assessments Section 9.5.1.5.10
Revised timing of initial C-SSRS from Baseline to Screening	Operational efficiencies	Table 2 Section 9.3.2 Section 9.5.1.5.10
Correct formatting of Synopsis, Other Secondary Objectives	Consistency	Synopsis – Objectives Section 8.2
Revised exclusion criteria for viral hepatitis (B or C) (#17) whereby active testing will not be performed	To clarify that the subjects will be excluded if they are known to have active hepatitis (B or C). Hepatitis (B or C) tests will not be conducted for the screening purpose.	Synopsis – Exclusion Criteria Section 9.3.2
Added footnotes regarding collection of PK samples at EOT and Early Discontinuation visits	To ensure appropriate timing of sampling relative to administration of last dose of study drug	Table 2
Added clarification for Unscheduled visits, such that they may be conducted at any time that additional assessments are clinically indicated in the judgment of the investigator.	Provide additional guidance to investigators	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Added clarification that prolactin testing should be fasting	Clarification	Table 2
Added requirement for pregnancy test and AM serum cortisol to Early Discontinuation Visit	Correction	Table 2 Table 3
Added requirement for lifestyle modification counseling Visit at Week 16	To ensure all visits are 4 weeks apart	Table 2
General alignment of text throughout	Clarity	Throughout

Revision History

Previous Version (Revision): v4.0

Current Version (Revision): v5.0

Date of Revisions: 22 Feb 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis - Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis - Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis - Study Protocol Title Synopsis - Design Synopsis - Inclusion Criteria Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Other Secondary Objectives Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.3.2 Section 9.5.1.5.10 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis - Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis - Other Secondary Objectives Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis - Other Secondary Objectives Synopsis - Efficacy Assessments Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Removed Appendix 3	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History

Previous Version (Revision): v2.0

Current Version (Revision): v3.0

Date of Revisions: 14 Sep 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis - Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Synopsis - Analysis Sets Synopsis - Pharmacodynamic Analyses Synopsis - Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Section 9.3.1
The secondary efficacy objective and endpoint were revised	To explore the predictability of 12-week responders for long-term sustainable weight loss effect	Synopsis - Secondary Efficacy Objectives Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis - Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis - Study Protocol Title Synopsis - Objectives Synopsis - Study Design Synopsis - Inclusion Criteria Synopsis - Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.10 Section 9.7.1.6 Section 9.7.1.8
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis - Efficacy Assessments Synopsis - Pharmacokinetic Assessments Synopsis - Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.1

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Change to primary and key secondary endpoints	Per FDA request	Synopsis - Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis - Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis - Exclusion Criteria Synopsis - Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision) v6.0 17 May 2017 (per Amendment 01) v7.0 11 Jul 2017 (per Amendment 02) V8.0 12 Dec 2017 (per Amendment 03)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

TBD

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting glucose, hemoglobin A_{1c} (HbA1C), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) in subjects with Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on fasting glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on body fat and lean mass composition by Dual-enerygy X-ray Absorptiometry (DEXA) in a subset of randomized subjects (selected prio to randomization) at selected sites during 52 weeks of

treatment (revised per Amendment 03)

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition with the Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by Centers for Disease Control and Prevention (CDC) growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass, and total body lean mass using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites, valvular function, and pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developed to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling. (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 30 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendment 03)

Study sites will be selected to ensure adequate representation of adolescents of ethnic and racial minorities. (revised per Amendment 03)

Data Monitoring Committee (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established.

Number of Subjects

Approximately 500 subjects will be screened to provide 260 randomized subjects. (revised per Amendment 02)

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of

T2DM.

Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and confirmed:

- HbA1c ≥6.5%
- fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With Type 2 diabetes who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

   In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
   - Left ventricular ejection fraction <45%
   - Intracardiac mass, tumor or thrombus
   - Evidence of congenital heart disease

- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:

    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

    - selective serotonin reuptake inhibitors (SSRIs)
    - serotonin norepinephrine reuptake inhibitors (SNRIs)
    - tricyclic antidepressants (TCAs)
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - linezolid
    - dextromethorphan in any form (eg, OTC cold medicines)
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

    b) Others

    - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
    - oral steroids (topical and inhaled steroids are acceptable)
    - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
    - benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening

19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
27. Planned bariatric surgery during the study or prior bariatric surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are

prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.
- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more anti-hyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or pulumonary hypertension (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendment 03)

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction.
- Waist circumference (revised per Amendment 03)
- Total body fat mass and total body lean mass will be determined centrally using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites at Baseline and Week 52/EOT (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

Pharmacokinetic Assessments

Blood samples (approximately 4 mL each) for PK assessment will be collected at Weeks 12, 28, 36, and 52 for analysis of Population PK. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit,but to bring their study drug to the clinic visit, and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing), and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for for PK assessments will be collected. Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (fasting glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea,

changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed.

Other Safety Assessments

Effect on growth will be evaluated using the CDC growth chart and bone age determination by x-ray of the hand. Sexual maturation will be evaluated by assessing sex hormones and Tanner Staging.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognition will be assessed using the Leiter-3. (revised per Amendment 01)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites. (revised per Amendment 03)

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed only for subjects at selected sites. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity. (revised per Amendment 03)

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from Baseline to Week 52 for subjects with Type 2 diabetes as baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for subjects with

Type 2 diabetes as baseline (revised per Amendment 03)

- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for the subjects without Type 2 diabetes at baseline (revised per Amendment 03)
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subjects compliance rate at each visit by pill count during 52 week treatment (revised per Amendment 03)

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at

Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White) and age. Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate.

Other Safety Analyses

In addition, cognition will be evaluated by the Leiter-3, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary

hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendments 01 and 03)

Abbreviation	Term
ADA	American Diabetes Association
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DEXA	Dual-energy X-ray Absorptiometry
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
Leiter-3	Leiter-3 International Performance Scale

Abbreviation	Term
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OGTT	oral glucose tolerance test
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PH	pulmonary hypertension
PHQ-9	Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal

Abbreviation	Term
US	United States
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity has become a global epidemic, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects

(Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies may be used in the present study to help retain participants. These include a highly trained and competent site staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, sites may utilize fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters to further encourage subject retention. Furthermore, we may make home visits for primary efficacy assessments of, as needed, to maximize data collection. By incorporating some of these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the

studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of

variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 260 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat sibutramine, and liraglutide 3 mg) (FDA, 2003; Chanoine, et al., 2005; Berkowitz, et al, 2006; CT.gov NCT02918279) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007). (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

- To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo (revised per Amendment 01)
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on fasting glucose, hemoglobin A1c (HbA1c), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) in subjects with Type 2 diabetes at baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on fasting glucose, HbA1c, insulin levels, and HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405 in subjects without Type 2 Diabetes at Baseline during 52 weeks of treatment (revised per Amendment 03)
  - Effects on body fat and lean mass composition by Dual-enerygy X-ray Absorptiometry (DEXA) in a subset of randomized subjects (selected prior to randomization) at selected sites during 52 weeks of treatment (revised per Amendment 03)
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]), systolic and diastolic blood pressure, and heart rate) during 52 weeks of treatment (revised per Amendment 03)

- To assess the safety of Belviq XR, including the effects on cognition by Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by CDC growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, bone mineral density and content, total body fat mass and total body lean mass by DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites, valvular function, pulmonary arterial pressure. (revised per Amendments 01 and 03)
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or matched placebo QD in a 1:1 ratio for up to 52 weeks. A recruitment plan will be developled to ensure at least 20% of younger subjects (12 to 13 years of age) are enrolled in the study. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2). (revised per Amendments 02 and 03)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be rescreened only once after 30 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on study drug at the end of the study. (revised per Amendment 03)

Study sites will be selected to ensure adequate representation of adolescents of ethinic and racial minorities. (revised per Amendment 03)

A Data Monitoring Committee (DMC) will be established to monitor and conduct periodic safety review of unblinded data. DMC members will be chosen based on their expertise in evaluating these clinical events. A separate DMC charter will be established. (revised per Amendment 03)

9.1.1 Prerandomization Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief

description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed

to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 260 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg. (revised per Amendment 02)

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 500 subjects will be screened to ensure that 260 subjects will be randomized. (revised per Amendment 02)

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened immediately without repeating the screening echocardiogram for up to 90 days after the previous echocardiogram. All other screening assessments must be repeated when a subject is re-screened. Subjects that re-screen more than 90 days after the previous echocardiogram must repeat all screening assessments including the screening echocardiogram. (revised per Amendment 03)

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old (inclusive) at Screening, with an initial BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg. Subjects with T2DM may have a pre-existing or new diagnosis of T2DM.

   Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM.

   Subjects with a new diagnosis of T2DM (ie, diagnosed at Screening) should be based on the 2016 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and then confirmed:
   - HbA1c ≥6.5%
   - fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA1c <10% at Screening. If subjects are being or need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. Minimal changes are defined as a change without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 03)

2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Who cannot swallow investigational products
3. With Type 2 diabetes who have hypoglycemia unawareness (revised per Amendment 03)
4. Any of the following findings on screening echocardiography:

   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
     - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a

RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, bipolar disorder, or schizophrenia
7. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
8. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
9. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year; inhaled steroids will be allowed) (revised per Amendment 03)
10. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
11. Use of any of the following medications:
    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
        - selective serotonin reuptake inhibitors (SSRIs)
        - serotonin norepinephrine reuptake inhibitors (SNRIs)
        - tricyclic antidepressants (TCAs)
        - bupropion
        - triptans
        - St. John's Wort
        - tryptophan
        - linezolid
        - dextromethorphan in any form (eg, OTC cold medicines)
        - lithium
        - tramadol
        - antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

12. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
13. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
14. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
15. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
16. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
17. History of alcohol or drug dependence or abuse
18. Recreational drug use within 2 years before Screening
19. Known to be human immunodeficiency virus (HIV) positive
20. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
21. Malignancy within 5 years before Screening
22. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
23. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
24. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
25. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
26. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent

27. Planned bariatric surgery during the study or prior bariatic surgical procedures (revised per Amendment 03)
28. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
29. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
30. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Investigators should do their best to bring all subject who discontinued early from the study in for the their primary endpoint collection regardless of the reason for ED. (revised per Amendment 01)

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL). For information on dosing on visits associated with PK sampling, see Section 9.5.1.4.1. (revised per Amendment 03)

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin (note that subjects should not be enrolled as indicated in exclusion criteria), or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.

- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or cessation of 1 or more anti-hyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

To minimize the risk of cardiac valve toxicity, subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. (revised per Amendment 01) If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits. (revised per Amendment 03)

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Subjects will be asked to bring their study drug bottles to each visit. The CRAs will review treatment compliance during site visits and at the completion of the study. (revised per Amendment 03)

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol

- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur

at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 URINE DRUG SCREEN

A 30-mL urine sample will be collected at Screening, as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines). (revised per Amendment 01)

9.5.1.3 Efficacy Assessments

- Body weight and height: will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI. Body weight will be measured in the morning after at least 8 hours of fasting and voiding using a calibrated scale and standardized instructions for clothing (ie, a hospital gown). Weight will be measured to the nearest 0.1 kg. Height will be measured in triplicate utilizing a stadiometer with a standardized process (eg, subjects should not be wearing shoes). Height must be measured to the nearest 0.1 cm. BMI will then be used to calculate the proportion (%) of subjects achieving at least a 5% and at least a 10% BMI reduction. (revised per Amendment 03)

- Waist circumference: will be determined by measurement taken with a tape measure positioned horizontally, parallel to the floor, at one finger width above the iliac crest. The subject should be standing erect with relaxed abdominal muscles. The tape measure should be snug but not compress the skin. The waist circumference should be taken to the nearest 1.0 cm, at the end of normal expiration. Three measurements will be taken and the average will be calculated. (revised per Amendment 03)
- Total body fat mass and total body lean mass: will be determined centrally using DEXA in a subset of randomized subjects (selected prior to randomization at selected sites) at Baseline and Week 52/EOT (revised per Amendment 03)
- Measurement of systolic and diastolic BP, heart rate (taken after resting for 5 minutes), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, HbA_{1c}, and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52 (revised per Amendment 03)
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

Every effort will be made to ensure that at least 80% of randomized subjects will have an assessment of the primary efficacy endpoint regardless of whether or not the subject remained on study drug or completed other study assessments. (revised per Amendment 03)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for Population PK analyses. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood

sample for PK assessment will be collected**.** Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Lorcaserin plasma exposure from PK analysis and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (fasting glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, fasting prolactin level will be measured and assessed. (revised per Amendment 03)

Bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset of randomized subjects (selected prior to randomization) at selected sites. (revised per Amendment 03)

9.5.1.5.1 **ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

At each visit, the investigator should actively assess as to whether any of the following adverse events have occurred during the interval since the last visit:

- Serotonin syndrome and signs or symptoms of serotonergism
- Signs or symptoms of valvular heart disease or pulmonary hypertension, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur

- Impairments in attention and memory, and confusion, somnolence, and fatigue
- Psychiatric disorders
- Hypoglycemia in subjects with diabetes on concomitant anti-diabetes medications (using ADA definitions)
- Priapism and hyperprolactinemia signs and symptoms should be recorded at each visit and whenever reported
- Hypersensitivity reactions

Any such events should be recorded as adverse events. Serotonin syndrome, valvular heart disease, pulmonary hypertension, and priapism should always be reported as serious adverse events (SAEs) (See Section 9.5.1.5.2 for a complete list of adverse events that should always be considered as Serious). (revised per Amendment 03)

Events of hypoglycemia in subjects with diabetes on concomitant anti-diabetes medication should be captured as per Section 9.5.2. Severe symptomatic events of hypoglycemia should always be reported as an SAE as per Section 9.5.1.5.2. (revised per Amendment 03)

It is the responsibility of the investigator to review the results of the Leiter-3, C-SSRS, and PHQ-9 for all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.10 for a description of the C-SSRS). (revised per Amendment 01)

All AEs must be monitored until symptom resolution, or until the condition stabalizes. (revised per Amendment 03)

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
- Severe symptomatic hypoglycemia (revised per Amendment 03)

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in

the study. Laboratory testing should be conducted on an unscheduled basis if clinically indicated. (revised per Amendment 03)

Table 1 Clinical Laboratory Tests (revised per Amendments 01 and 03)

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium, bicarbonate
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	AM serum Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects)
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other (revised per Amendment 01)	Albumin, calcium, globulin, fasting glucose, HbA_{1c}, HDL cholesterol, fasting insulin, lactate dehydrogenase, LDL cholesterol, fasting lipid panel, phosphorus, total protein, total cholesterol, triglycerides,, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained in triplicate to the nearest 0.1 cm as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.1.5.6 CDC GROWTH MEASUREMENTS

Investigators will calculate the height for age percentile and weight for age percentile utilizing the most recent CDC 95th Percentile Growth Chart and the height and weight measurements obtained, as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.7 WAIST CIRCUMFERENCE

Waist circumference (cm) measurements will be obtained in triplicate to the nearest 1.0 cm taken 3 times at each visit as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendments 01 and 03)

9.5.1.5.8 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

As part of the physical examination, a neuromuscular sign assessment for serotonin syndrome will be performed for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF. (revised per Amendment 01)

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will also be captured in the AE eCRF. (revised per Amendment 01)

9.5.1.5.9 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.10 OTHER SAFETY ASSESSMENTS

Leiter-3

The Leiter International Performance Scale–Third Edition (Leiter-3) is widely used non verbal measure of intelligence, memory, and attention in those between the ages of 3 and 75 years. The Attention/Memory Battery consists of 5 subtests: 2 measure nonverbal attention; 2 measure memory; and 1 measures cognitive interference (nonverbal Stroop test). These subtests are combined to produce a Memory and Processing Speed composite scores, normalized to a mean of 100 and standard deviation of 15. The Leiter-3 will be used to assess lorcaserin effects on cognition, specifically, attention and memory. In addition, signs and symptoms of cognition-related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF. (revised per Amendment 01)

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. Qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and

certification process for administering the C-SSRS. It will be performed at Screening and at study visits as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

DEXA for the Assessment of Bone Mineral Density

Bone mineral density body composition determination by DEXA whole body composition, to include bone mineral density and content, total body fat mass and total body lean mass will be determined using DEXA in a subset subjects (selected prior to randomization) at selected sites. A contracted vendor will provide all administration and project management services for DEXA scanning. This will include site and image data management services, as well as site training and certification. (revised per Amendment 03)

A miminum of 30 subjects ages 12-18 years (selected prior to randomization) should have bone density evaluated with DEXA at BL and week 52/EOT. (revised per Amendment 03)

Hand X-Ray

A hand x-ray for evaluation of any potential negative effect on bone age will be performed on the same hand at each visit as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of subjects will be using Tanner Staging by a trained clinician (Marshall, 1970). Subjects will be examined by the investigator as designated in the Schedules/Assessments (Table 2). (revised per Amendments 01 and 03)

Echocardiogram

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery systolic pressure will be estimated from the TR regurgitant jet velocity. (revised per Amendment 03)

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at every visit as specified in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 03)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks[d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[e]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging		X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X	X	X	X		X		X			X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, insulin, and HbA1c sampling	X	X				X		X			X			X
T4 and TSH	X	X						X			X			X
Testosterone, Estradiol		X						X			X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks[d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (urine)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting prolactin	X	X				X		X			X		X	X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X		X	X		X[f]		X[g]	X[f]
AM serum cortisol		X									X			X
ECG		X						X			X	X		
Echocardiograph	X[h]							X			X			
DEXA[i]		X												X
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Hand x-ray for bone age		X									X			X
C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Leiter-3		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01, 02 and 03)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment[b]**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[c]	ED
Day:	-30 to -1	1												
Weeks[d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Standardized age-appropriate lifestyle modification counseling[j]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, SAE = serious adverse event; T4 = thyroxine, TSH = thyroid stimulating hormone, US = unscheduled.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits. (revised per Amendments 01 and 03)
Unscheduled visits may be conducted at any time that additional assessments are indicated in the clinical judgment of the investigator. Note that not all assessments listed under Unscheduled Visit need to be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs. At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendments 01 and 03)

c: On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessments will be collected Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

d: Includes a neuromuscular assessment for serotonin syndrome, and signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) (revised per Amendments 01 and 03)

e: PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug.

f: PK samples should only be collected if subject has experienced an SAE while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE.

g: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

h: Only subjects in selected sites will have this assessment done. (revised per Amendment 03)

i: Lifestyle modification counseling will also be performed at Weeks 3, 16, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Appendix 2.

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9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes (revised per Amendments 01 and 03)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), EOS or ED	5×8=40
T4, TSH, AM Serum Cortisol, Testosterone, estradiol	6	Screening: 1 Visits 2, 8, 11 (EOT), or ED	6×4=24
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or ED	8×3=24
Fasting Prolactin, FPG, fasting insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or ED, US	5×6=30
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or ED (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			146

ED= early discontinuation from study, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, OC = osteocalcin, PD = pharmacodynamic, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious

criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms (revised per Amendment 03)
- Fibroadenomas of the breast or ductal carcinoma in situ
-
- Severe symptomatic hypoglycemia (revised per Amendment 03)

Subject-reported episodes of hypoglycemia or decreased blood sugar should be captured on the eCRF according to the following guidelines:

- Psuedo-hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level. (revised per Amendment 03)
- Probable symptomatic hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)
- Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L) (revised per Amendment 03)
- Documented symptomatic hypoglycemia: An event during which typical hypoglycemia symptoms are accompanied by a measured plasma glucose ≤70 mg/dL (≤3.9 mmol/L) (revised per Amendment 03)

- Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitation actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (revised per Amendment 03)

See Section 9.4.6 (Prior and Concomitant Therapy) for directions on the recommendations for possible adjustment to antihyperglycemic medication doses in response to reported episodes of hypoglycemia. (revised per Amendment 03)

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue study drug prematurely will continue to be evaluated on for all study assessments until study completion. All attempts will be made to capture height and weight in all subjects whether or not they are still on IP at the end of the study. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments Table 2). (revised per Amendment 03)

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be contacted by

mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of the secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF. If "lost to follow-up" is recorded in clinical data base, appropriate queries will be sent to investigators in order to collect all the relevant reasons for missing data. (revised per Amendment 03)

Every effort, including proper training of all study participants and their parent/guardian, should be made in order to achieve optimal subject retention and prevent missing data, especially for the Week 52 primary endpoint. A retention plan to help avoid missing data will be developed and included in study manual. (revised per Amendment 03)

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH

guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12

- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in total body composition (total fat and lean mass) in a subset of randomized subjects at end of 52 weeks of treatment (revised per Amendment 03)
- Change in HbA_{1c} from Baseline to Week 52 for subjects with Type 2 diabetes at baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for subjects with Type 2 diabetes at baseline (revised per Amendment 03)
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52 for the subjects without Type 2 diabetes at baseline (revised per Amendment 03)
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52
- Subject compliance rate at each visit by pill count during 52 weeks of treatement (per Amendment 03)

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) on the FAS for study treatment compared to placebo, as appropriate. The model will include all data and will include treatment, time, and the interaction of treatment by time as fixed effects, with adjustment for sex (male versus female), BMI and age at baseline, and subject as a random effect. (revised per Amendment 03)

Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The MMRM model assumes that the missing data are missing at random and

makes use of all available data even if a subject has missing data at some post-baseline visits. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. (revised per Amendment 03)

Categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White), and age. Additional subgroups may be explored, if deemed necessary. (revised per Amendment 03)

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment for serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, vital sign measurements, bone mineral density and content, total body fat mass and total body lean mass will be summarized by treatment group using descriptive statistics or frequency count as appropriate. (revised per Amendments 01 and 03)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also

compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, study drug effect on cognition assessed by Leiter-3, assessment of suicidality using C-SSRS, depression assessment using PHQ-9, bone mineral density and content, total body fat mass, and total body lean mass using DEXA will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by

echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52. (revised per Amendments 01 and 03)

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number: APD356-A001-403

Study Protocol Title: A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigational Product Name: APD356/Belviq XR® (lorcaserin hydrochloride)

IND Number: 069888

SIGNATURES

Authors:

PPD

Date

Neurology Business Group
Eisai Inc.

PPD

Date

PPD Medicine Development Group
Eisai Inc.

PPD

Date

Neurology Business Group
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Revision): v6.0 Current Version (Revision): v7.0 Date of Revisions: 11 Jul 2017 (per Amendment 02)		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised statistical power from 90% to 80%	80% statistical power would provide sufficent sample size to detect weight loss effects and evaluate lorcaserin safety in the population selected.	Synopsis – Study Design Synopsis – Number of Subjects Synopsis – Sample Size Rationale Section 7.1.2 Section 9.1 Section 9.2 Section 9.3 Section 9.7.2
Revised Other Secondary Endpoints	To align with recently submitted PPSR	Synopsis – Other Secondary Efficacy Endpoints Section 9.7.1.1.2
Added clarification on timing of PK samples taken during an early discontinuation visit	Clarification	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Revised scale for measuring of cognition from Wide Range Assessment of Memory and Learning-2 (WRAML-2) to Leiter-3	Leiter-3 is selected to replace WRAML-2 for the evaluation of the change in cognition for the following reasons:Lack of availability of WRAML-2 in Spanish, Leiter-3's high scientific validity, non-verbal format to offer less biased assessment for subjects whose second language is English, easier and shorter administration and short test time reducing investigator burden, as well as increase probability of the subjects' retention in the study.	Synopsis – Objectives Synopsis – Other Safety Assessments Synopsis – Other Safety Analyses List of Abbreviations Section 8.2 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Added requirement that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS	To provide guidance that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.	Synopsis – Other Safety Assessments Section 9.5.1.5.10
Revised timing of initial C-SSRS from Baseline to Screening	Operational efficiencies	Table 2 Section 9.3.2 Section 9.5.1.5.10
Correct formatting of Synopsis, Other Secondary Objectives	Consistency	Synopsis – Objectives Section 8.2
Revised exclusion criteria for viral hepatitis (B or C) (#17) whereby active testing will not be performed	To clarify that the subjects will be excluded if they are known to have active hepatitis (B or C). Hepatitis (B or C) tests will not be conducted for the screening purpose.	Synopsis – Exclusion Criteria Section 9.3.2
Added footnotes regarding collection of PK samples at EOT and Early Discontinuation visits	To ensure appropriate timing of sampling relative to administration of last dose of study drug	Table 2
Added clarification for Unscheduled visits, such that they may be conducted at any time that additional assessments are clinically indicated in the judgment of the investigator.	Provide additional guidance to investigators	Table 2
Added clarification that prolactin testing should be fasting	Clarification	Table 2

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Added requirement for pregnancy test and AM serum cortisol to Early Discontinuation Visit	Correction	Table 2 Table 3
Added requirement for lifestyle modification counseling Visit at Week 16	To ensure all visits are 4 weeks apart	Table 2
General alignment of text throughout	Clarity	Throughout

Revision History

Previous Version (Revision): v4.0

Current Version (Revision): v5.0

Date of Revisions: 22 Feb 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis - Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis - Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis - Study Protocol Title Synopsis - Design Synopsis - Inclusion Criteria Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Other Secondary Objectives Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.3.2 Section 9.5.1.5.10 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis - Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis - Other Secondary Objectives Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis - Other Secondary Objectives Synopsis - Efficacy Assessments Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Removed Appendix 3	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History

Previous Version (Revision): v2.0

Current Version (Revision): v3.0

Date of Revisions: 14 Sep 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis - Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Synopsis - Analysis Sets Synopsis - Pharmacodynamic Analyses Synopsis - Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Section 9.3.1
The secondary efficacy objective and endpoint were revised	To explore the predictability of 12-week responders for long-term sustainable weight loss effect	Synopsis - Secondary Efficacy Objectives Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis - Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis - Study Protocol Title Synopsis - Objectives Synopsis - Study Design Synopsis - Inclusion Criteria Synopsis - Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.10 Section 9.7.1.6 Section 9.7.1.8
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis - Efficacy Assessments Synopsis - Pharmacokinetic Assessments Synopsis - Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.1

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Change to primary and key secondary endpoints	Per FDA request	Synopsis - Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis - Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis - Exclusion Criteria Synopsis - Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision) v6.0 17 May 2017 (per Amendment 01) v7.0 11 Jul 2017 (per Amendment 02)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment.
- To assess the safety of Belviq XR, including the effects on cognition with the Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by

Centers for Disease Control and Prevention (CDC) growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, valvular function, and pulmonary arterial pressure.(revised per Amendment 01)

- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling. (revised per Amendment 02)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately500 subjects will be screened to provide260 randomized subjects. (revised per Amendment 02)

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient

>25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)

- Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
6. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
7. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
8. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year)
9. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
10. Use of any of the following medications:

    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

    - selective serotonin reuptake inhibitors (SSRIs)
    - serotonin norepinephrine reuptake inhibitors (SNRIs)
    - tricyclic antidepressants (TCAs)
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - linezolid
    - dextromethorphan in any form (eg, OTC cold medicines)
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

    b) Others

    - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
    - oral steroids (topical and inhaled steroids are acceptable)
    - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
    - benzodiazepines

11. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening,

including but not limited to pergolide, ergotamine, methysergide, and cabergoline

12. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
13. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
14. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
15. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
16. History of alcohol or drug dependence or abuse
17. Recreational drug use within 2 years before Screening
18. Known to be human immunodeficiency virus positive
19. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
20. Malignancy within 5 years before Screening
21. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
22. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
23. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
24. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
25. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
26. Planned bariatric surgery during the study
27. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
28. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
29. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52

- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Blood samples (approximately 4 mL each) for PK assessment will be collected at Weeks 12, 28, 36, and 52 for analysis of Population PK. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit,but to bring their study drug to the clinic visit, and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing), and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for for PK assessments will be collected. Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (fasting glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed.

Other Safety Assessments

Effect on growth will be evaluated using the CDC growth chart and bone age determination by x-ray of the hand. Sexual maturation will be evaluated by assessing sex hormones and Tanner Staging.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognition will be assessed using the Leiter-3. (revised per Amendment 01)

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate.

Other Safety Analyses

In addition, cognition will be evaluated by the Leiter-3, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendment 01)

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
Leiter-3	Leiter-3 International Performance Scale
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PHQ-9	The Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity has become a global epidemic, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects

(Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Furthermore, we will make home visits for assessments of families, as needed, to maximize data collection. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be

used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis

demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of260 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat sibutramine, and liraglutide 3 mg) (FDA, 2003; Chanoine, et al., 2005; Berkowitz, et al, 2006; CT.gov NCT02918279) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007). (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

- To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo (revised per Amendment 01)
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognition by Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by CDC growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health assessments valvular function, pulmonary arterial pressure. (revised per Amendment 01)
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling

- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 260 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (130 subjects) and placebo (130 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2). (revised per Amendment 02)

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be rescreened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 260 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg. (revised per Amendment 02)

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 500 subjects will be screened to ensure that 260 subjects will be randomized. (revised per Amendment 02)

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
    a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
    b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on screening echocardiography:
    - Aortic regurgitation mild or greater

- Mitral regurgitation moderate or greater
- Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
- Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
  - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, bipolar disorder, or schizophrenia
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year)
9. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
10. Use of any of the following medications:
    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
       - selective serotonin reuptake inhibitors (SSRIs)
       - serotonin norepinephrine reuptake inhibitors (SNRIs)
       - tricyclic antidepressants (TCAs)
       - bupropion

- triptans
- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

11. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
12. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
13. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
14. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
15. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
16. History of alcohol or drug dependence or abuse
17. Recreational drug use within 2 years before Screening
18. Known to be human immunodeficiency virus positive
19. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
20. Malignancy within 5 years before Screening
21. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
22. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)

23. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
24. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
25. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
26. Planned bariatric surgery during the study
27. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
28. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
29. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Investigators should do their best to bring all subject who discontinued early from the study in for the their primary endpoint collection regardless of the reason for ED. (revised per Amendment 01)

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number

5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is

being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study

supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 URINE DRUG SCREEN

A 30-mL urine sample will be collected at Screening, as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines). (revised per Amendment 01)

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for Population PK analyses. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessment will be collected**.** Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Lorcaserin plasma exposure from PK analysis and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (fasting glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed.

9.5.1.5.1 **ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or

symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the Leiter-3, C-SSRS, and PHQ-9 for all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.10 for a description of the C-SSRS). (revised per Amendment 01)

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose,

misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests (revised per Amendment 01)

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	AM serum Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects)
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other (revised per Amendment 01)	Albumin, calcium, globulin, fasting glucose, HbA_{1c}, HDL cholesterol, fasting insulin, lactate dehydrogenase, LDL cholesterol, fasting lipid panel, phosphorus, total protein, total cholesterol, triglycerides,, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated

method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 CDC GROWTH MEASUREMENTS

Investigators will calculate the height for age percentile and weight for age percentile utilizing the most recent CDC 95th Percentile Growth Chart and the height and weight measurements obtained, as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.7 WAIST CIRCUMFERENCE

Waist circumference (cm) measurements will be taken 3 times at each visit as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.8 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

As part of the physical examination, a neuromuscular sign assessment for serotonin syndrome will be performed for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF. (revised per Amendment 01)

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will also be captured in the AE eCRF. (revised per Amendment 01)

9.5.1.5.9 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.10 OTHER SAFETY ASSESSMENTS

Leiter-3

The Leiter International Performance Scale–Third Edition (Leiter-3) is widely used non verbal measure of intelligence, memory, and attention in those between the ages of 3 and 75 years. The Attention/Memory Battery consists of 5 subtests: 2 measure nonverbal attention; 2 measure memory; and 1 measures cognitive interference (nonverbal Stroop test). These subtests are combined to produce a Memory and Processing Speed composite scores, normalized to a mean of 100 and standard deviation of 15. The Leiter-3 will be used to assess lorcaserin effects on cognition, specifically, attention and memory. In addition, signs and symptoms of cognition-related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF. (revised per Amendment 01)

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. Qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS. It will be performed at Screening and at study visits as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

Hand X-Ray

A hand x-ray for evaluation of any potential negative effect on bone age will be performed on the same hand at each visit as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of subjects will be using Tanner Staging (Marshall, 1970). Subjects will be examined by the investigator as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Echocardiogram

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR regurgitant jet velocity.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01 and 02)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[e]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X	X	X	X		X		X			X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, insulin, and HbA1c sampling	X	X				X		X			X			X
T4 and TSH	X							X			X			X
Testosterone, Estradiol	X							X			X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01 and 02)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (urine)	X	X	X	X	X	X	X	X	X	X	X	X		X
Fasting prolactin	X	X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X		X	X		X[f]		X[g]	X[f]
AM serum cortisol		X									X			X
ECG		X						X			X	X		X
Echocardiograph	X[h]							X			X			X
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Hand x-ray for bone age		X				X		X			X			X
C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Leiter-3		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized age-appropriate lifestyle modification counseling[i]		X	X	X	X	X	X	X	X	X			X	

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendments 01 and 02)

Phase:	Prerandomization[a]	Randomization												
Period:	Screening	Treatment										Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, SAE = serious adverse event; T4 = thyroxine, TSH = thyroid stimulating hormone, US = unscheduled.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Unscheduled visits may be conducted at any time that additional assessments are indicated in the clinical judgment of the investigator. Note that not all assessments listed under Unscheduled Visit need to be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs. At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

c: Window ±7 days for all visits. (revised per Amendment 01)

d: On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessments will be collected Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

e: Includes a neuromuscular assessment and signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) (revised per Amendment 01)

f: PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug.

g: PK samples should only be collected if subject has experienced an SAE while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE.

h: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

i: Lifestyle modification counseling will also be performed at Weeks 3, 16, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Appendix 2.

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9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes (revised per Amendment 01)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), EOS or ED	5×8=40
T4, TSH, AM Serum Cortisol, Testosterone, estradiol	6	Screening: 1 Visits 8, 11 (EOT), or ED	6×3=18
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or ED	8×3=24
Fasting Prolactin, FPG, fasting insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or ED	5×5=25
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or ED (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			135

ED= early discontinuation from study, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, OC = osteocalcin, PD = pharmacodynamic, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious

criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

  The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken

code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Association between change and percentage change in BMI from Baseline to Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Association between the proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 with the outcome of achieving at least a 5% BMI reduction at Week 12 (revised per Amendment 02)
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from

baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, study drug effect on cognition assessed by Leiter-3, assessment of suicidality using C-SSRS, and depression assessment using PHQ-9 will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52. (revised per Amendment 01)

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 260 subjects in a 1:1 ratio (n=130 in the Belviq XR 20-mg treatment group; n=130 in the placebo group) will have at least 80% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 260 subjects (130 subjects for Belviq XR 20 mg and 130 subjects for placebo) will also have greater than 78% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Chi-Square test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects. (revised per Amendment 02)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number: APD356-A001-403

Study Protocol Title: A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigational Product Name: APD356/Belviq XR® (lorcaserin hydrochloride)

IND Number: 069888

SIGNATURES

Authors:

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Eisai Inc.

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History

Previous Version (Revision): v5.0

Current Version (Revision): v6.0

Date of Revisions: 17 May 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Revised scale for measuring of cognition from Wide Range Assessment of Memory and Learning-2 (WRAML-2) to Leiter-3	Leiter-3 is selected to replace WRAML-2 for the evaluation of the change in cognition for the following reasons:Lack of availability of WRAML-2 in Spanish, Leiter-3's high scientific validity, non-verbal format to offer less biased assessment for subjects whose second language is English, easier and shorter administration and short test time reducing investigator burden, as well as increase probability of the subjects' retention in the study.	Synopsis – Objectives Synopsis – Other Safety Assessments Synopsis – Other Safety Analyses List of Abbreviations Section 8.2 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Added requirement that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS	To provide guidance that qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.	Synopsis – Other Safety Assessments Section 9.5.1.5.10
Revised timing of initial C-SSRS from Baseline to Screening	Operational efficiencies	Table 2 Section 9.3.2 Section 9.5.1.5.10
Correct formatting of Synopsis, Other Secondary Objectives	Consistency	Synopsis – Objectives Section 8.2
Revised exclusion criteria for viral hepatitis (B or C) (#17) whereby active testing will not be performed	To clarify that the subjects will be excluded if they are known to have active hepatitis (B or C). Hepatitis (B or C) tests will not be conducted for the screening purpose.	Synopsis – Exclusion Criteria Section 9.3.2
Added footnotes regarding collection of PK samples at EOT and Early Discontinuation visits	To ensure appropriate timing of sampling relative to administration of last dose of study drug	Table 2
Added clarification for Unscheduled visits, such that they may be conducted at any time that additional assessments are clinically indicated in the judgment of the investigator.	Provide additional guidance to investigators	Table 2
Added clarification that prolactin testing should be fasting	Clarification	Table 2

Revision History Previous Version (Revision): v5.0 Current Version (Revision): v6.0 Date of Revisions: 17 May 2017 (per Amendment 01)		
Change	**Rationale**	**Affected Protocol Section(s)**
Added requirement for pregnancy test and AM serum cortisol to Early Discontinuation Visit	Correction	Table 2 Table 3
Added requirement for lifestyle modification counseling Visit at Week 16	To ensure all visits are 4 weeks apart	Table 2
General alignment of text throughout	Clarity	Throughout

Revision History

Previous Version (Revision): v4.0

Current Version (Revision): v5.0

Date of Revisions: 22 Feb 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis - Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis - Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis - Study Protocol Title Synopsis - Design Synopsis - Inclusion Criteria Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Other Secondary Objectives Synopsis - Exclusion Criteria Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.3.2 Section 9.5.1.5.10 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6

Revision History

Previous Version (Revision): v3.0

Current Version (Revision): v4.0

Date of Revisions: 03 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis - Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis - Other Secondary Objectives Synopsis - Safety Assessments Synopsis - Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis - Primary Efficacy Analysis Section 9.7.1.6
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis - Other Secondary Objectives Synopsis - Efficacy Assessments Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Removed Appendix 3	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History

Previous Version (Revision): v2.0

Current Version (Revision): v3.0

Date of Revisions: 14 Sep 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis - Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Synopsis - Analysis Sets Synopsis - Pharmacodynamic Analyses Synopsis - Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis - Inclusion Criteria Section 9.3.1
The secondary efficacy objective and endpoint were revised	To explore the predictability of 12-week responders for long-term sustainable weight loss effect	Synopsis - Secondary Efficacy Objectives Synopsis - Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis - Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis - Study Protocol Title Synopsis - Objectives Synopsis - Study Design Synopsis - Inclusion Criteria Synopsis - Assessments Synopsis - Efficacy Analyses Synopsis - Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.10 Section 9.7.1.6 Section 9.7.1.8
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis - Efficacy Assessments Synopsis - Pharmacokinetic Assessments Synopsis - Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.10 Section 9.7.1.8 Section 9.7.1.8.1

Revision History

Previous Version (Original Protocol): v1.0

Current Version (Revision): v2.0

Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Change to primary and key secondary endpoints	Per FDA request	Synopsis - Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis - Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis - Exclusion Criteria Synopsis - Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision) v6.0 17 May 2017 (per Amendment 01)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment.
- To assess the safety of Belviq XR, including the effects on cognition with the Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by

Centers for Disease Control and Prevention (CDC) growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health, valvular function, and pulmonary arterial pressure.(revised per Amendment 01)

- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater

- Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
- Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
6. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
7. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
8. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year)
9. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
10. Use of any of the following medications:

a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- bupropion
- triptans
- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others

- antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
- benzodiazepines

11. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
12. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
13. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
14. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
15. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
16. History of alcohol or drug dependence or abuse
17. Recreational drug use within 2 years before Screening
18. Known to be human immunodeficiency virus positive
19. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
20. Malignancy within 5 years before Screening
21. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
22. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
23. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
24. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
25. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
26. Planned bariatric surgery during the study
27. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
28. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
29. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Blood samples (approximately 4 mL each) for PK assessment will be collected at Weeks 12, 28, 36, and 52 for analysis of Population PK. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit,but to bring their study drug to the clinic visit, and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing), and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for for PK assessments will be collected. Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (fasting glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed.

Other Safety Assessments

Effect on growth will be evaluated using the CDC growth chart and bone age determination by x-ray of the hand. Sexual maturation will be evaluated by assessing sex hormones and Tanner Staging.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognition will be assessed using the Leiter-3. (revised per Amendment 01)

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass

spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in

BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a

5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate.

Other Safety Analyses

In addition, cognition will be evaluated by the Leiter-3, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendment 01)

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
Leiter-3	Leiter-3 International Performance Scale
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PHQ-9	The Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity has become a global epidemic, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects

(Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Furthermore, we will make home visits for assessments of families, as needed, to maximize data collection. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be

used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis

demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, et al, 2005; Berkowitz, et al, 2006) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

- To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo (revised per Amendment 01)
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognition by Leiter-3 International Performance Scale (Leiter-3), depression with the Patient Health Questionnaire (PHQ-9), signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), growth measured by CDC growth chart, sexual maturation (pubescence) measured by Tanner Staging scores, and other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health assessments valvular function, pulmonary arterial pressure. (revised per Amendment 01)
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling

- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be rescreened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 360 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
    a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
    b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on screening echocardiography:
    - Aortic regurgitation mild or greater
    - Mitral regurgitation moderate or greater

- Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
- Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
  - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, bipolar disorder, or schizophrenia
6. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS.
7. Any suicidal behavior in the past based on the C-SSRS (revised per Amendment 01)
8. Known secondary causes (genetic, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year)
9. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
10. Use of any of the following medications:
    a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
       - selective serotonin reuptake inhibitors (SSRIs)
       - serotonin norepinephrine reuptake inhibitors (SNRIs)
       - tricyclic antidepressants (TCAs)
       - bupropion
       - triptans

- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

11. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
12. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
13. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
14. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
15. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
16. History of alcohol or drug dependence or abuse
17. Recreational drug use within 2 years before Screening
18. Known to be human immunodeficiency virus positive
19. Known to have active viral hepatitis (B or C) (revised per Amendment 01)
20. Malignancy within 5 years before Screening
21. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
22. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
23. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization

24. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
25. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
26. Planned bariatric surgery during the study
27. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
28. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
29. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

    (NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Investigators should do their best to bring all subject who discontinued early from the study in for the their primary endpoint collection regardless of the reason for ED. (revised per Amendment 01)

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number

5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is

being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study

supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 URINE DRUG SCREEN

A 30-mL urine sample will be collected at Screening, as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines). (revised per Amendment 01)

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for Population PK analyses. (revised per Amendment 01)

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. (revised per Amendment 01)

On the day of the Week 36 clinic visit, subjects will take their study drug **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessment will be collected**.** Dose times must be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Lorcaserin plasma exposure from PK analysis and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (fasting glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and hyperprolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed.

9.5.1.5.1 **ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or

symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the Leiter-3, C-SSRS, and PHQ-9 for all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.10 for a description of the C-SSRS). (revised per Amendment 01)

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose,

misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests (revised per Amendment 01)

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	AM serum Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects)
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other (revised per Amendment 01)	Albumin, calcium, globulin, fasting glucose, HbA_{1c}, HDL cholesterol, fasting insulin, lactate dehydrogenase, LDL cholesterol, fasting lipid panel, phosphorus, total protein, total cholesterol, triglycerides,, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated

method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 CDC GROWTH MEASUREMENTS

Investigators will calculate the height for age percentile and weight for age percentile utilizing the most recent CDC 95th Percentile Growth Chart and the height and weight measurements obtained, as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.7 WAIST CIRCUMFERENCE

Waist circumference (cm) measurements will be taken 3 times at each visit as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

9.5.1.5.8 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

As part of the physical examination, a neuromuscular sign assessment for serotonin syndrome will be performed for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF. (revised per Amendment 01)

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will also be captured in the AE eCRF. (revised per Amendment 01)

9.5.1.5.9 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.10 OTHER SAFETY ASSESSMENTS

Leiter-3

The Leiter International Performance Scale–Third Edition (Leiter-3) is widely used non verbal measure of intelligence, memory, and attention in those between the ages of 3 and 75 years. The Attention/Memory Battery consists of 5 subtests: 2 measure nonverbal attention; 2 measure memory; and 1 measures cognitive interference (nonverbal Stroop test). These subtests are combined to produce a Memory and Processing Speed composite scores, normalized to a mean of 100 and standard deviation of 15. The Leiter-3 will be used to assess lorcaserin effects on cognition, specifically, attention and memory. In addition, signs and symptoms of cognition-related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF. (revised per Amendment 01)

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. Qualified personnel must evaluate positive responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS. It will be performed at Screening and at study visits as designated in the Schedule of Procedures/Assessments (Table 2). (revised per Amendment 01)

Hand X-Ray

A hand x-ray for evaluation of any potential negative effect on bone age will be performed on the same hand at each visit as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of subjects will be using Tanner Staging (Marshall, 1970). Subjects will be examined by the investigator as designated in the Schedules/Assessments (Table 2). (revised per Amendment 01)

Echocardiogram

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR regurgitant jet velocity.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendment 01)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[e]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X	X	X	X		X		X			X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, fasting insulin, and HbA1c sampling	X	X				X		X			X			X
T4 and TSH	X							X			X			X
Testosterone, Estradiol	X							X			X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendment 01)

Phase:	**Prerandomization[a]**	**Randomization**												
Period:	**Screening**	**Treatment**										**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (urine)	X	X	X	X	X	X	X	X	X	X	X	X		X
Prolactin (fasting)	X	X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X		X	X		X[f]		X[g]	X
AM serum cortisol		X									X			X
ECG		X						X			X	X		X
Echocardiograph	X[h]							X			X			X
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Hand x-ray for bone age		X				X		X			X			X
C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X
Leiter-3		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized age-appropriate lifestyle modification counseling[i]		X	X	X	X	X	X	X	X	X			X	

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403 (revised per Amendment 01)

Phase:	Prerandomization[a]	Randomization												
Period:	Screening	Treatment										Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	US[b]	ED
Day:	-30 to -1	1												
Weeks[c,d]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, SAE = serious adverse event; T4 = thyroxine, TSH = thyroid stimulating hormone, US = unscheduled.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Unscheduled visits may be conducted at any time that additional assessments are indicated in the clinical judgment of the investigator. Note that not all assessments listed under Unscheduled Visit need to be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs. At Unscheduled Visits, PK samples should only be collected if subject has experienced a serious adverse event (SAE) while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE. (revised per Amendment 01)

c: Window ±7 days for all visits. (revised per Amendment 01)

d: On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed not to take their study drug at home before the visit, but to bring their study drug to the clinic visit and take their daily dose **at the clinic**. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: 1 predose (within 30 minutes before dosing) and 1 within 1 to 3 hours after dosing. Dose times must be recorded for the last 2 dosing times before the day of clinic visit. Week 52 PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug. On the day of the Week 36 clinic visit, subjects will take the morning dose **at home**, and will be asked to visit the clinic within 4 to 6 hours of dosing that day, during which 1 blood sample for PK assessments will be collected Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit. (revised per Amendment 01)

e: Includes a neuromuscular assessment and signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) (revised per Amendment 01)

f: PK samples should only be collected if the sample can be drawn within 60 hours of the last dose of study drug.

g: PK samples should only be collected if subject has experienced an SAE while on study drug and the sample can be drawn within 60 hours of the initiation of the SAE.

h: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

i: Lifestyle modification counseling will also be performed at Weeks 3, 16, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Appendix 2.

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9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes (revised per Amendment 01)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), EOS or ED	5×8=40
T4, TSH, AM Serum Cortisol, Testosterone, estradiol	6	Screening: 1 Visits 8, 11 (EOT), or ED	6×3=18
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or ED	8×3=24
Fasting Prolactin, FPG, fasting insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or ED	5×5=25
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or ED (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			135

ED= early discontinuation from study, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, OC = osteocalcin, PD = pharmacodynamic, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious

criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

  The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken

code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from Baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant

medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD endpoint. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination, neuromuscular sign assessment, and signs and symptoms of priapism and hyperprolactinemia), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. (revised per Amendment 01)

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from

baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, study drug effect on cognition assessed by Leiter-3, assessment of suicidality using C-SSRS, and depression assessment using PHQ-9 will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52. (revised per Amendment 01)

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number: APD356-A001-403

Study Protocol Title: A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigational Product Name: APD356/Belviq XR® (lorcaserin hydrochloride)

IND Number: 069888

SIGNATURES

Authors:

PPD

Date

Neurology Business Group
Eisai Inc.

PPD

Date

PPD Medicine Development Group
Eisai Inc.

PPD

Date

Neurology Business Group
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Revision): v4.0 Current Version (Revision): v5.0 Date of Revisions: 22 Feb 2017		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
A full physical examination will be performed at Week 1	Correction	Synopsis • Safety Assessment Section 9.5.1.5
PHQ-9 questionnaire has been added to every scheduled visit.	Per FDA recommendation	Synopsis • Safety Assessment Section 9.5.1.5 Section 9.5.2.1
The mixed model repeated measures (MMRM) model was replaced with the analysis of covariance (ANCOVA) model analyzing Week 52 only.	Per FDA recommendation	Synopsis • Primary Efficacy Analysis Section 9.7.1.6
All postdiscontinuation data will be used in the primary analysis	Clarification per FDA feedback	Synopsis • Primary Efficacy Analysis Section 9.7.1.6
Labeling information for study drug was updated	Correction as the study will only be conducted in the US	Section 9.4.2.3
The order of assessments was reorganized in the Schedule of Assessments	To better align the assessments by grouping them	Section 9.5.2.1
Urinalysis will be performed at Visit 2 instead of Visit 9	Correction	Section 9.5.2.1
Assessment for testosterone, estradiol will be performed at Week 28, not Week 20	Correction	Section 9.5.2.1 Section 9.5.2.3
Prior/concomitant medication assessment will be performed at Week 56	Correction	Section 9.5.2.1

Revision History Previous Version (Revision): v4.0 Current Version (Revision): v5.0 Date of Revisions: 22 Feb 2017		
Change	**Rationale**	**Affected Protocol Section(s)**
Assessments performed at early discontinuation from the study	Correction	Section 9.5.2.1
Summary of blood volumes table was updated	Correction	Section 9.5.2.3

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis • Study Protocol Title • Study Design • Inclusion Criteria • Exclusion Criteria • Safety Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis • Other Secondary Objectives • Exclusion Criteria • Safety Assessments • Safety Analyses Section 8.2

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
		Section 9.3.2 Section 9.5.1.5.8 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis • Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis • Other Secondary Objectives • Safety Assessments • Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.9 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis • Primary Efficacy Analysis Section 9.7.1.6

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis • Other Secondary Objectives • Efficacy Assessments • Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Appendix 3 removed	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis • Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria • Analysis Sets • Pharmacodynamic Analyses • Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria Section 9.3.1
The secondary efficacy objective	To explore the predictability of 12-week	Synopsis • Secondary Efficacy Objectives

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
and endpoint were revised	responders for long-term sustainable weight loss effect	• Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis • Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis • Study Protocol Title • Objectives • Study Design • Inclusion Criteria • Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.9 Section 9.7.1.6 Section 9.7.1.8

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis • Efficacy Assessments • Pharmacokinetic Assessments • Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.9 Section 9.7.1.8 Section 9.7.1.8.1
Change to primary and key secondary endpoints	Per FDA request	Synopsis • Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis • Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision) v5.0 22 Feb 2017 (Revision)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

- Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment
- Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin

Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment. To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on depression by the Patient Health Questionnaire (PHQ-9), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by Centers for Disease Control and Prevention (CDC) growth chart, on sexual maturation (pubescence) measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, valvular function and pulmonary arterial pressure, adrenal function, bone age, and biochemical markers of bone health assessments
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized,

reduced-calorie diet and an age-appropriate, increased physical activity program

4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

   In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

   - Left ventricular ejection fraction <45%
   - Intracardiac mass, tumor or thrombus
   - Evidence of congenital heart disease
   - Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)
4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
6. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, known genetic causes of obesity)

7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
8. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - linezolid
   - dextromethorphan in any form (eg, OTC cold medicines)
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

   b) Others

   - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
   - oral steroids (topical and inhaled steroids are acceptable)
   - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
   - benzodiazepines

9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
10. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
11. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
12. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
13. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
14. History of alcohol or drug dependence or abuse
15. Recreational drug use within 2 years before Screening
16. Known to be human immunodeficiency virus positive
17. Active viral hepatitis (B or C) as demonstrated by positive serology
18. Malignancy within 5 years before Screening

19. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
20. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
21. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
22. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
23. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
24. Planned bariatric surgery during the study
25. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
26. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
27. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52

- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Plasma lorcaserin concentrations will be measured at Weeks 12, 28, 36, and 52 for analysis of population PK. All subjects will be instructed to take their study drug in the morning on the day before their scheduled clinic visit at Weeks 12, 28, 36, and 52. No additional doses should be taken that day for those subjects who have been taking their doses in the evening. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing.

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**. One blood sample for determination of plasma concentrations of lorcaserin will be collected at the clinic within 4 to 6 hours after dosing.

Subjects can resume their usual dose schedule the day after the PK clinic visits.

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and prolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination, at Baseline, Weeks 1, 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 at every visit and effects on cognitive

function will be assessed using the WRAML-2 at Baseline, Weeks 5, 28, 52, and end of study (EOS).

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography method coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using

a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging),

out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, cognitive function will be evaluated by the WRAML-2, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra-individual comparisons. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate.

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random

Abbreviation	Term
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PHQ-9	The Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WRAML-2	Wide Range Assessment of Memory and Learning-2

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity

Obesity has become a global epidemic in western civilization, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in

adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects (Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Furthermore, we will make home visits for assessments of families, as needed, to maximize data collection. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body

weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI

in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, et al, 2005; Berkowitz, et al, 2006) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on depression by the Patient Health Questionnaire (PHQ-9), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by CDC growth chart, on sexual maturation (pubescence) measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, valvular function, pulmonary arterial pressure, adrenal function, bone age, and biochemical markers of bone health assessments
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling

- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization/Pretreatment Phase

Screening will occur during the Prerandomization Phase at Visit 1

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization/Treatment Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 360 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
    a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
    b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on screening echocardiography:
    - Aortic regurgitation mild or greater

- Mitral regurgitation moderate or greater
- Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
- Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
  - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
6. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)
7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
8. Use of any of the following medications:
   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
      - selective serotonin reuptake inhibitors (SSRIs)
      - serotonin norepinephrine reuptake inhibitors (SNRIs)
      - tricyclic antidepressants (TCAs)

- bupropion
- triptans
- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
10. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
11. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
12. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
13. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
14. History of alcohol or drug dependence or abuse
15. Recreational drug use within 2 years before Screening
16. Known to be human immunodeficiency virus positive
17. Active viral hepatitis (B or C) as demonstrated by positive serology
18. Malignancy within 5 years before Screening
19. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation

20. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
21. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
22. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
23. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
24. Planned bariatric surgery during the study
25. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
26. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
27. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \bullet 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country. As the study is being conducted in US only, the study drug label will be printed in English.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a

calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and

Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs
    - SSRIs
    - SNRIs
    - TCAs
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - MAOIs
    - linezolid
    - dextromethorphan
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

b. Others
    - antiseizure medications including valproic acid, zonisamide, and lamotrigine
    - oral steroids (topical or inhaled steroids are acceptable)
    - stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
    - benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or

shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
    - Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
    - Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for population PK analyses. All subjects will be instructed to take their study drug in the morning on the day before their scheduled clinic visit at Weeks 12, 28, 36, and 52. No additional doses should be taken that day for those subjects who have been taking their doses in the evening. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing.

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home.** One blood sample for determination of plasma concentration of lorcaserin will be collected at the clinic within 4 to 6 hours after dosing.

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Blood samples will be collected to determine lorcaserin plasma exposure and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and prolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination at Baseline, Weeks 1, 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior at every visit. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 at every visit, and effects on cognitive function will be assessed using the WRAML-2 at Baseline, Weeks 5, 28, 52, and EOS.

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated

laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS, PHQ-9, and WRAML-2 in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event

- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior

- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time

points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects),
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other	Albumin, calcium, globulin, glucose, HbA_{1c}, HDL cholesterol, lactate dehydrogenase, LDL cholesterol, phosphorus, total protein, total cholesterol, triglycerides, prolactin, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.8 ECHOCARDIOGRAM

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

9.5.1.5.9 OTHER SAFETY ASSESSMENTS

WRAML-2

The WRAML-2 administration will consist of the Core Battery, which provides scores on Verbal Memory, Visual Memory, and Attention/Concentration. There are 6 subtests (2 for each area). The tests provide standardized scores based on age and gender, and are appropriate for ages 5 to 90 years. The WRAML-2 will be used to assess lorcaserin effects on cognitive function. In addition, signs and symptoms of cognitive related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF.

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. It will be performed at Baseline and at study visits as designated in the Schedule of Procedures/Assessments (Table 2).

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will be captured in the eCRF.

Hand X-Ray will be evaluated for any potential negative effect on bone age as designated in the Schedules/Assessments (Table 2). Neuromuscular sign assessment for serotonin syndrome will be performed as designated in the Schedule of Procedures/Assessments (Table 2) to screen for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation from study
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[d]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X	X	X	X		X		X			X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, fasting	X	X				X		X			X			X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation from study
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
insulin, and HbA1c sampling														
T4 and TSH	X							X			X			X
Testosterone, Estradiol	X							X			X			
Pregnancy test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X		
Prolactin	X	X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Fasting lipid panel		X						X			X			X
Urine NTX		X						X			X			X
PK/PD blood sampling						X		X	X		X			X
AM serum cortisol		X									X			
ECG		X						X			X	X		X
Echocardiograph	X[f]							X			X			X
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	Prerandomization[a]		Randomization										Other	
Period:	Screening		Treatment									Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation from study
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Hand x-ray for bone age		X				X		X			X			X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X
WRAML-2		X		X				X			X	X		X
PHQ-9		X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized age-appropriate lifestyle modification counseling[e]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PD = pharmacodymanic, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone, WRAML-2 = Wide Range Assessment of Memory and Learning-2.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits after Visit 2 except for Weeks 12 and 28 (the window for these visits will be broader at ±14 days). Week is shown unless otherwise indicated.

c: On the day of the Week 12, 28, and 52 clinic visits, subjects will take their morning dose of study drug on the day before their scheduled clinic visit. On the day of the clinic visit, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: predose (within 30 minutes before dosing) and within 1 to 3 hours after dosing. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

d: Includes a neuromuscular assessment

e: Lifestyle modification counseling will also be performed at Weeks 3, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Table 2.

f: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests (Chemistry and Hematology)	5	Screening: 1 Visits 2, 3, 4, 6, 8, 11 (EOT), or Early discontinuation from study, EOS	5×8=40
T4, TSH, Cortisol, Testosterone, estradiol	6	Screening: 1 Visits 8, 11 (EOT), or Early discontinuation from the study	6×3=18
Serum OC and PICP, Hydroxy-proline; Fasting lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)	8	Visits 2, 8, 11 (EOT), or Early discontinuation from the study	8×3=24
Fasting Prolactin, FPG, Insulin, and HbA_{1c} sampling	5	Screening: 1 Visits 2, 6, 8, 11 (EOT) or Early discontinuation from the study	5×5=25
PK/PD blood sampling	4	Visits 6, 8, and 11 (EOT) or Early discontinuation from the study (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			135

EOS = End of Study; EOT = End of Treatment; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; OC = osteocalcin; PD = pharmacodynamic; PICP = carboxyterminal propeptide of type I procollagen; PK = pharmacokinetics; T4 = thyroxine; TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

  The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from Baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52

- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using analysis of covariance model (ANCOVA) with factors of treatment, sex (male and female) as fixed effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values will be imputed at each visit using all available values including the retrieved measurement from the postdiscontinuation data. The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, cognitive function will be evaluated by the WRAML-2, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate.

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, neuromuscular sign assessment for serotonin syndrome, signs and symptoms of priapism and prolactinemia, study drug effect on cognitive function assessed by WRAML-2, assessment of suicidality using C-SSRS, and depression assessment using PHQ-9 will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52.

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

SIGNATURES

Authors:

PPD

Date

Neuroscience Business Group

Eisai Inc.

PPD

Date

Eisai Inc.

PPD

Date

Neuroscience Business Group

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Subject population to include children ages 12 to 17 years	Changes were made upon regulatory advice received at the Type C meeting.	Title Page Synopsis • Study Protocol Title • Study Design • Inclusion Criteria • Exclusion Criteria • Safety Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.7.1.6 Section 9.7.1.8 Protocol Signature Page Investigator Signature Page
All subjects will be evaluated for cardiac valvular disease or pulmonary hypertension via echocardiographic assessment.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis • Other Secondary Objectives • Exclusion Criteria • Safety Assessments • Safety Analyses Section 8.2

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
		Section 9.3.2 Section 9.5.1.5.8 Section 9.5.2 Section 9.7.1.8 Section 9.7.1.8.6
Study drug administration will be taken at approximately the same time each day. On the days of PK sampling and the day before the subjects come to the clinic for PK sampling, study drug will be taken in the morning and doses recorded 2 days prior to the clinic visit.	This will ensure lower variability with regard to PK/PD measurements.	Synopsis • Pharmacokinetic Assessments Section 9.4.1 Section 9.4.4 Section 9.5.1.4.1 Section 9.5.2.1
Screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the Patient Health Questionnaire (PHQ-9), and not the Children's Depression Inventory 2 (CDI-2).	The PHQ-9 was originally proposed by the FDA for the population in the current study.	Synopsis • Other Secondary Objectives • Safety Assessments • Safety Analyses Section 8.2 Section 9.5.1.5 Section 9.5.2 Section 9.5.1.5.1 Section 9.5.1.5.9 Section 9.7.1.8 Section 9.7.1.8.6
Primary analysis changed from MMRM to using a pattern mixture model utilizing multiple imputations (MI) to impute missing values.	Changes were made upon regulatory advice received at the Type C meeting.	Synopsis • Primary Efficacy Analysis Section 9.7.1.6

Revision History Previous Version (Revision): v3.0 Current Version (Revision): v4.0 Date of Revisions: 03 Nov 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Clarified fasting lipids	Fasting lipid levels provide uniformity in lipid measurements for definition of dyslipidemia	Synopsis • Other Secondary Objectives • Efficacy Assessments • Other Secondary Efficacy Endpoints Section 8.2 Section 9.5.1.3
Appendix 3 removed	The current study will not conduct any biomarker or pharmacogenomic evaluation. PK/PD measurements will be done during study.	Appendix 3

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis • Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria • Analysis Sets • Pharmacodynamic Analyses • Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria Section 9.3.1
The secondary efficacy objective	To explore the predictability of 12-week	Synopsis • Secondary Efficacy Objectives

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
and endpoint were revised	responders for long-term sustainable weight loss effect	• Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis • Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History
Previous Version (Original Protocol): v1.0
Current Version (Revision): v2.0
Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis • Study Protocol Title • Objectives • Study Design • Inclusion Criteria • Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.9 Section 9.7.1.6 Section 9.7.1.8

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis • Efficacy Assessments • Pharmacokinetic Assessments • Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.9 Section 9.7.1.8 Section 9.7.1.8.1
Change to primary and key secondary endpoints	Per FDA request	Synopsis • Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis • Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision) v4.0 03 Nov 2016 (Revision)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

- Approximately 24 months from the 1st subject enrolled to last subject's last visit or last assessment
- Phase 4

Objectives

Primary Objective

- To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin

Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment. To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on depression by the Patient Health Questionnaire (PHQ-9), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by Centers for Disease Control and Prevention (CDC) growth chart, on sexual maturation (pubescence) measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, valvular function and pulmonary arterial pressure, adrenal function, bone age, and biochemical markers of bone health assessments
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized,

reduced-calorie diet and an age-appropriate, increased physical activity program

4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on Screening echocardiography:
   - Aortic regurgitation mild or greater
   - Mitral regurgitation moderate or greater
   - Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
   - Systolic pulmonary artery pressure (SPAP) >40 mmHg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)

   In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.

   - Left ventricular ejection fraction <45%
   - Intracardiac mass, tumor or thrombus
   - Evidence of congenital heart disease
   - Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)
4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
6. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, known genetic causes of obesity)

7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
8. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - linezolid
   - dextromethorphan in any form (eg, OTC cold medicines)
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

   b) Others

   - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
   - oral steroids (topical and inhaled steroids are acceptable)
   - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
   - benzodiazepines

9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
10. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
11. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
12. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
13. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
14. History of alcohol or drug dependence or abuse
15. Recreational drug use within 2 years before Screening
16. Known to be human immunodeficiency virus positive
17. Active viral hepatitis (B or C) as demonstrated by positive serology
18. Malignancy within 5 years before Screening

19. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
20. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
21. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
22. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
23. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
24. Planned bariatric surgery during the study
25. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
26. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
27. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: up to 30 days

Randomization Phase: approximately 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52

- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Plasma lorcaserin concentrations will be measured at Weeks 12, 28, 36, and 52 for analysis of population PK. All subjects will be instructed to take their study drug in the morning on the day before their scheduled clinic visit at Weeks 12, 28, 36, and 52. No additional doses should be taken that day for those subjects who have been taking their doses in the evening. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing.

On the day of the Week 36 clinic visit, subjects will take their study drug in the morning **at home**. One blood sample for determination of plasma concentrations of lorcaserin will be collected at the clinic within 4 to 6 hours after dosing.

Subjects can resume their usual dose schedule the day after the PK clinic visits.

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, metabolic function (glucose, fasting lipids, and thyroid), adrenal function and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and prolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination, at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognitive function will be assessed using

WRAML-2.

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the TR jet velocity.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography method coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the repeated measures analysis of covariance model (ANCOVA) with factors of treatment visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), , sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) using the same model as the analysis model. The missing values will be imputed for a visit at a time using the complete cases up to and include the current visit for a particular visit. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model. As a sensitivity analysis, the missing values will also be imputed using pattern mixture MI method assuming the missing value is missing not at random (MNAR). The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, cognitive function will be evaluated by the WRAML-2, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate.

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random

Abbreviation	Term
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PHQ-9	The Patient Health Questionnaire
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
RVOTAT	right ventricular outflow tract
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SPAP	systolic pulmonary artery pressure
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WRAML-2	Wide Range Assessment of Memory and Learning-2

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity

Obesity has become a global epidemic in western civilization, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters, et al., 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese adolescents are likely to become tomorrow's obese adults (Whitaker, et al., 1997).

Current approaches to weight management in adults include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals, including adolescents. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise, but are rarely used for adolescents.

The current standard of care for treatment of obesity in adolescent subjects ranges from behavioral therapy including lifestyle intervention to the rare use of pharmacotherapy in

adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects (Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Furthermore, we will make home visits for assessments of families, as needed, to maximize data collection. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body

weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for adolescent subjects with body weight greater than 60 kg.

In adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States. It is also intended to support an indication for chronic weight management for obese adolescents ages 12 to 17 years old.

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese adolescents.

In the Phase 3 orlistat study in obese adolescents mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI

in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, et al, 2005; Berkowitz, et al, 2006) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L]/405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) including fasting lipid changes (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL]) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on depression by the Patient Health Questionnaire (PHQ-9), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by CDC growth chart, on sexual maturation (pubescence) measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, valvular function, pulmonary arterial pressure, adrenal function, bone age, and biochemical markers of bone health assessments
- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling

- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents ages 12 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by sex. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes a standardized, age-appropriate diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization/Pretreatment Phase

Screening will occur during the Prerandomization Phase at Visit 1

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization/Treatment Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (ages 12 to 17 years old) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric or adolescent subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of subjects who are older than 12 years of age having a body weight of less than 60 kg is very low; therefore, the current study as designed to enroll subjects between 12 to 17 years of age with body weight at least 60 kg, will cover majority of the population of interest. The targeted study population comprises 360 obese adolescents 12 to 17 years of age, with a body weight at least 60 kg.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, ages 12 to 17 years old at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg
2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a standardized, reduced-calorie diet and an age-appropriate, increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
    a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
    b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Any of the following findings on screening echocardiography:
    - Aortic regurgitation mild or greater

- Mitral regurgitation moderate or greater
- Mitral or aortic valve stenosis greater than mild (ie, aortic stenosis [AS]: jet >3.0 m/s, mean gradient >25 mm Hg, and aortic valve area [AVA] <1.5 cm^2; MS: mean gradient >5 mm Hg and mitral valve area [MVA] <1.5 cm^2)
- Systolic pulmonary artery pressure (SPAP) >40 mm Hg (and/or tricuspid regurgitation (TR) jet velocity >2.9 m/s)
  - In cases where an actual SPAP value is not measurable due to lack of adequate TR jet, the pulmonary flow acceleration time measured at the right ventricular outflow tract (RVOTAT), will be used to assess eligibility. Patients with a RVOTAT ≤100 msec will be excluded, suggesting an elevated mean SPAP; eligibility for the those patients with RVOTAT between 100 and 120 msec will be determined based on combined assessment of the TR jet, septal motion and right ventricular size.
- Left ventricular ejection fraction <45%
- Intracardiac mass, tumor or thrombus
- Evidence of congenital heart disease
- Clinically significant pericardial effusion (eg, moderate or larger or with hemodynamic compromise)

4. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
5. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
6. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)
7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
8. Use of any of the following medications:
   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
      - selective serotonin reuptake inhibitors (SSRIs)
      - serotonin norepinephrine reuptake inhibitors (SNRIs)
      - tricyclic antidepressants (TCAs)

- bupropion
- triptans
- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others
- antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
10. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
11. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
12. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
13. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
14. History of alcohol or drug dependence or abuse
15. Recreational drug use within 2 years before Screening
16. Known to be human immunodeficiency virus positive
17. Active viral hepatitis (B or C) as demonstrated by positive serology
18. Malignancy within 5 years before Screening
19. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation

20. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
21. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
22. Subjects with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
23. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
24. Planned bariatric surgery during the study
25. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
26. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
27. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD at approximately the same time each day.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \bullet 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a

calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily at approximately the same time of every day, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and

Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs
    - SSRIs
    - SNRIs
    - TCAs
    - bupropion
    - triptans
    - St. John's Wort
    - tryptophan
    - MAOIs
    - linezolid
    - dextromethorphan
    - lithium
    - tramadol
    - antipsychotics or other dopamine antagonists

b. Others
    - antiseizure medications including valproic acid, zonisamide, and lamotrigine
    - oral steroids (topical or inhaled steroids are acceptable)
    - stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
    - benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or

shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using a standard stadiometer method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
    - Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
    - Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for population PK analyses. All subjects will be instructed to take their study drug in the morning on the day before their scheduled clinic visit at Weeks 12, 28, 36, and 52. No additional doses should be taken that day for those subjects who have been taking their doses in the evening. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

On the day of the Week 12, 28, and 52 clinic visits, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing.

On the day of the Week 36 clinic visit, subjects will take their study drug at home in the morning in the morning **at home.** One blood sample for determination of plasma concentration of lorcaserin will be collected at the clinic within 4 to 6 hours after dosing.

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Blood samples will be collected to determine lorcaserin plasma exposure and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluations for hematology, metabolic function (glucose, lipids, and thyroid), adrenal functions, and biochemical blood and urine bone health assessments; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and prolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up.

The C-SSRS will be used to assess all subjects in the study for any signal of depression or suicidal ideation or behavior. Additionally, screening, diagnosing, monitoring, and measuring the severity of depression will be assessed using the PHQ-9 and effects on cognitive function will be assessed using WRAML-2.

Echocardiographic assessments will be used to exclude subjects with FDA-defined valvulopathy, pulmonary hypertension, and other major cardiovascular disease (as outlined in Exclusion Criterion No. 3) during the Screening Period. Additionally, cardiac valvular function and pulmonary systolic pressure changes at Weeks 28 and 52 will be assessed. Valvular regurgitation as assessed in the echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated

laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS, PHQ-9, and WRAML-2 in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event

- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior

- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time

points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects),
Bone health assessments	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other	Albumin, calcium, globulin, glucose, HbA_{1c}, HDL cholesterol, lactate dehydrogenase, LDL cholesterol, phosphorus, total protein, total cholesterol, triglycerides, prolactin, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.8 ECHOCARDIOGRAM

Echocardiograms will be obtained on the Schedule of Procedures/Assessments (Table 2). Valvular regurgitation in echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

9.5.1.5.9 OTHER SAFETY ASSESSMENTS

WRAML-2

The WRAML-2 administration will consist of the Core Battery, which provides scores on Verbal Memory, Visual Memory, and Attention/Concentration. There are 6 subtests (2 for each area). The tests provide standardized scores based on age and gender, and are appropriate for ages 5 to 90 years. The WRAML-2 will be used to assess lorcaserin effects on cognitive function. In addition, signs and symptoms of cognitive related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF.

PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 assigns weight to the degree to which depressive problems have affected the patient's level of function.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. It will be performed at Baseline and at study visits as designated in the Schedule of Procedures/Assessments (Table 2).

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will be captured in the eCRF.

Hand X-Ray will be evaluated for any potential negative effect on bone age as designated in the Schedules/Assessments (Table 2). Neuromuscular sign assessment for serotonin syndrome will be performed as designated in the Schedule of Procedures/Assessments (Table 2) to screen for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X		X	X
Inclusion/exclusion criteria	X	X												
Physical Examination[d]	X	X	X			X		X			X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X		X	X		X		X	X		X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, Fasting Insulin, HOMA-IR, and HbA_{1c} sampling	X	X				X		X			X			X
T4 and TSH	X							X			X			X
AM serum cortisol		X									X			
Testosterone, Estradiol	X						X				X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Pregnancy test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X						X			X	X		X
Echocardiograph	X[f]							X			X			X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X
WRAML-2		X		X				X			X	X		X
PHQ-9		X	X	X		X	X		X		X	X		X
Hand x-ray for bone age		X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Urine NTX		X						X			X			
PK/PD blood sampling						X		X	X		X			X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Prolactin	X							X			X			X
Standardized age-appropriate lifestyle modification counseling[e]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event, AM = morning; CDC = Centers for Disease Control and Prevention, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PHQ-9 = The Patient Health Questionnaire, PICP = carboxyterminal propeptide of type I procollagen, PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone, WRAML-2 = Wide Range Assessment of Memory and Learning-2.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits after Visit 2 except for Weeks 12 and 28 (the window for these visits will be broader at ±14 days). Week is shown unless otherwise indicated.

c: On the day of the Week 12, 28, and 52 clinic visits, subjects will take their morning dose of study drug on the day before their scheduled clinic visit. On the day of the clinic visit, subjects will be instructed to take their study drug at approximately the same time as the morning before, with no additional doses taken that day. Two blood samples for determination of plasma concentrations of lorcaserin will be taken: predose (within 30 minutes before dosing) and within 1 to 3 hours after dosing. On the day of the Week 36 clinic visit, subjects will take the morning dose at home, and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing. Dose times **must** be recorded for the last 2 dosing times prior to the clinic visit.

d: Includes a neuromuscular assessment

e: Lifestyle modification counseling will also be performed at Weeks 3, 24, 32, 40, and 48 in addition to counseling at the scheduled visits in Table 2.

f: Echocardiographic assessments will be performed during screening period after subjects have met all other inclusion and exclusion criteria.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Visits 2, 3, 4, 6, 8; 11/EOT, EOS	12×8=96
T4, TSH, Cortisol, Testosterone, estradiol, Serum OC and PICP, Hydroxy-proline; Fasting prolactin levels	10	Screening: 1 Visits 8; 11/EOT/Early discontinuation	10×3=30
Prolactin, FPG, Insulin, and HbA_{1c} sampling	4	Screening: 1 Visits 2, 6, 8; 11/EOT/Early discontinuation	4×5=20
PK/PD blood sampling	4	Visits 6, 8, and 11/EOT/Early discontinuation (2 samples each); Visit 9 (1 sample only)	7×4=28
Total			174

EOS = End of Study; EOT = End of Treatment; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; OC = osteocalcin; PD = pharmacodynamic; PICP = carboxyterminal propeptide of type I procollagen; PK = pharmacokinetics; T4 = thyroxine; TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the

AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

  The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code

for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has

the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from Baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52

- Change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the repeated measures analysis of covariance model (ANCOVA) with factors of treatment, visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline age and BMI as covariates. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) using the same model as the analysis model. The missing values will be imputed for a visit at a time using the complete cases up to and include the current visit for a particular visit. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model. As a sensitivity analysis, the missing values will also be imputed using pattern mixture MI method assuming the missing value is missing not at random (MNAR). The details of the analysis model and missing value imputation method will be further described in the SAP.

In addition, the following analyses will also be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Subgroup analyses and additional sensitivity analyses, if appropriate, may also be performed and will be described in the SAP.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using mixed effect model repeated measurement analysis (MMRM) and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also be assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values, ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, cognitive function will be evaluated by the WRAML-2, depression will be evaluated by the PHQ-9, and suicidal ideation and behavior will be evaluated by the C-SSRS, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension [pulmonary hypertension is defined when the subject's systolic pulmonary artery pressure (SPAP) ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will be summarized by treatment group at Week 28 and Week 52 using descriptive statistics or frequency count as appropriate.

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including adolescent growth evaluations using 95th percentile CDC growth charts and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, neuromuscular sign assessment for serotonin syndrome, signs and symptoms of priapism and prolactinemia, study drug effect on cognitive function assessed by WRAML-2, assessment of suicidality using C-SSRS, and depression assessment using PHQ-9 will be summarized by treatment group at each scheduled visit. For echocardiographic assessments, the proportion of subjects who develop FDA-defined valvulopathy, the proportion of subjects who develop pulmonary hypertension (defined as when a subject's SPAP is ≥40 mmHg evaluated by echocardiograph], and change from baseline in SPAP will also be summarized by treatment group at Week 28 and Week 52.

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will be encouraged to participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

SIGNATURES

Authors:

PPD

Date

Neuroscience Business Group

Eisai Inc.

PPD

Date

Eisai Inc.

PPD

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Neuroscience Business Group

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Prehypertension was deleted from the inclusion criterion. Subjects with Stage 1 primary hypertension, with an upper limit defined as 99% plus 5 mmHg for age, sex, and height are included in the study.	Prehypertension does not qualify as a comorbid condition. The limitation on BP is to further define the proper study population.	Synopsis • Inclusion Criteria Section 9.3.1
Removed the restriction that subjects need to have less than 44 kg/m^2 BMI for study entry	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria • Analysis Sets • Pharmacodynamic Analyses • Pharmacokinetic/Pharmacodynamic Analyses Section 9.3.1 Section 9.7.1.7.2 Section 9.7.1.7.3
Removal of study entry requirement that the caregiver cannot have a history of ADD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia	Per United States Food and Drug Administration (FDA) request	Synopsis • Inclusion Criteria Section 9.3.1
The secondary efficacy objective	To explore the predictability of 12-week	Synopsis • Secondary Efficacy Objectives

Revision History Previous Version (Revision): v2.0 Current Version (Revision): v3.0 Date of Revisions: 14 Sep 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
and endpoint were revised	responders for long-term sustainable weight loss effect	• Other Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2
Subjects with symptoms or signs of cardiac valvular disease or pulmonary hypertension are not required to have further evaluation by centralized echocardiogram assessment. In addition, no adjudication will be performed. Local echocardiograms can be performed if deemed medically necessary by the investigator.	This change allows for the investigator to make the decision to perform local echocardiograms on a pediatric subject if deemed medically indicated rather than burden the subject to undergo a mandated, unnecessary procedure.	Synopsis • Safety Assessments Section 9.5.1.5
Updated study rationale	Clarification	Section 7.1.1.2

Revision History
Previous Version (Original Protocol): v1.0
Current Version (Revision): v2.0
Date of Revisions: 22 Jul 2016

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis • Study Protocol Title • Objectives • Study Design • Inclusion Criteria • Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.8 Section 9.7.1.6 Section 9.7.1.8

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis • Efficacy Assessments • Pharmacokinetic Assessments • Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.8 Section 9.7.1.8 Section 9.7.1.8.1
Change to primary and key secondary endpoints	Per FDA request	Synopsis • Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis • Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision) v3.0 14 Sep 2016 (Revision)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from first subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD.
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L] / 405) during 52 weeks of treatment

- Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) during 52 weeks of treatment

- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on mood by Children's Depression Inventory 2 (CDI-2), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by Centers for Disease Control and Prevention (CDC) growth chart, on sexual maturation measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health.
- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese children and adolescents, ages 9 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by age group and sex. At least 30% of the total subjects should be ages 9 to 11 years. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes diet and exercise counseling.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg

OR

Otherwise healthy male or female children, age 9 to 11 years at Screening, with a BMI that is greater than or equal to US-weighted mean of the 99th percentile based on age and sex, and a body weight greater than 60 kg associated with at least 1 co-morbid weight-related condition (eg, type 2 diabetes mellitus, hypertension, dyslipidemia)

- Type 2 Diabetes as defined by American Diabetes Association Standards of Diabetes Care, 2013.
- Stage 1 primary hypertension (blood pressure in the 95th to 99th percentile plus 5 mmHg for age, sex, and height) as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011) during the Screening Period
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a reduced-calorie diet and an increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension by objective assessments (ie, imaging modality or cardiac catheterization)
4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg, Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, known genetic causes of obesity)
8. Use of other products intended for weight loss including prescription drugs, over-the-counter

(OTC) drugs, and herbal preparations within 1 month before Screening

9. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - linezolid
   - dextromethorphan in any form (eg, OTC cold medicines)
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

   b) Others

   - antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
   - oral steroids (topical and inhaled steroids are acceptable)
   - stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
   - benzodiazepines

10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
14. Any use of a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before Screening
17. Known to be human immunodeficiency virus positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology
19. Malignancy within 5 years before Screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or

guardian to supervise study participation

21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
23. Subjects 12 to 17 years old with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects over 12 years old who had hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated, biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: 30 days

Randomization Phase: 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications, including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline

to Week 52

- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Plasma lorcaserin concentrations will be measured at Weeks 12, 28, 36, and 52 for analysis of population PK. At Weeks 12, 28, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing. At the Week 36 visit, subjects will take the morning dose at home, and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

Pharmacodynamic Assessments

- Change from baseline in BMI
- Proportion (%) of subjects achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, thyroid function, adrenal function and biochemical blood and urine biomarkers of bone health; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and prolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of children and adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination, at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Children and adolescent sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up. Any subject with symptoms or signs of cardiac valvular disease or pulmonary hypertension may be evaluated by local echocardiographic assessment at the discretion of the investigator if deemed medically indicated. The (C-SSRS) will be used to assess all children and adolescents in the study for any signal of depression or suicidal ideation or behavior. Additionally, mood will be assessed using the CDI-2 and effects on cognitive function will be assessed using WRAML-2.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography method coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the mixed effect model repeated measurement analysis (MMRM) assuming the missing data is missing at random (MAR), with factors of treatment visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), age group (9 to 11 years old and 12 to 17 years old), sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline BMI as a covariate. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model.

Subgroup analyses and additional sensitivity analyses will be performed as appropriate including multiple imputation methods assuming the missing values are MAR and missing not at random (MNAR) to handle missing data.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Multiple imputation (MI): the same primary efficacy analyses described above will be analyzed using MI for impute the missing data, assuming the missing values are MAR and MNAR.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Additional sensitivity analyses may also be explored and described in the SAP, if deemed appropriate.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, age group (9 to 11 years old and 12 to 17 years old), sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using MMRM and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as

needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including age group (9 to 11 years old and 12 to 17 years old), sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values (including biomarkers), ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, suicidal ideation, cognitive function, behavior, and mood will be evaluated by the C-SSRS, WRAML-2, CDI-2, and C-SSRS, respectively, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CDI-2	Children's Depression Inventory 2
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PI	principal investigator
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WRAML-2	Wide Range Assessment of Memory and Learning-2

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity

Obesity has become a global epidemic in western civilization, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). The prevalence of obesity in children in United States is also high. The United States Centers for Disease Control and Prevention (CDC) reported in 2012 that 17.7% of children ages 6 to 11 years are obese. Obesity in children and adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Childhood and adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters , et al, 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese children are likely to become tomorrow's obese adults.

Current approaches to weight management include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise.

The current standard of care for treatment of obesity in pediatric subjects ranges from lifestyle intervention in children less than 8 years of age to use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects (Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Further, we will make home visits for assessments for families, as needed, to maximize data collection. We anticipate achieving a 75% or greater retention rate at Month 12. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for children and adolescent subjects with body weight greater than 60 kg.

In preadolescent and adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States, as well as in children ages 9 to 11 years. It is also intended to support an indication for chronic weight management for obese children and adolescents ages 9 to 17 years.

It is intended to have 20 subjects treated with lorcaserin XR in each age group and 10 subjects on lorcaserin XR for 52 weeks in each age groups, which is well above the numbers of subjects in adolescent studies with other products (ie, ezetimibe combination therapy with reductase inhibitors in primary hypercholesterolemia and heterozygous familial hypercholesterolemia in study involved 10 to 17 years old). The total number of subjects at baseline for combination therapy was 5 subjects at age 10 years old and 9 subjects at age 11 years old group (FDA, 2007).

7.1.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for children and adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in older children (9 to 11 years of age) and obese adolescents, where weight loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese children and adolescents.

In the Phase 3 orlistat study in obese adolescents and children mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years, and none in children under the age of 9 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, et al, 2005; Berkowitz, et al, 2006) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate that achieving at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD is predictive of sustained change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L] / 405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg hypertension, dyslipidemia) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on mood by Children's Depression Inventory 2 (CDI-2), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by CDC growth chart, on sexual maturation measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health.
- To assess the PK of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and

probability of achieving at least a 5% and at least a 10% reduction in BMI from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese children and adolescents ages 9 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by age group and sex. At least 30% of total subjects should be ages 9 to 11 years for the reasons outlined above in Section 7.1.1.2. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization/Pretreatment Phase

Screening will occur during the Prerandomization Phase at Visit 1

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization/Treatment Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025 and healthy, obese pediatric subjects ages 6 to 11 years in Study APD356-A001-026. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (age 12 to 17 years) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was performed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of enrolling subjects who are younger than 9 years of age with body weight of at least 60 kg is low; therefore, the current study is designed to enroll the subjects between 9 to 17 years of age.

The targeted study population comprises 360 obese children and adolescents 9 to 17 years of age.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007). Obesity in children will be identified using gender- and age-specific BMI measurement. Obesity in children (9 to 11 years of age) is defined by The American Academy of Pediatrics 2007 recommendation as BMI in the 99th percentile and at least 1 co-morbidity (Spear, et al, 2007).

The proposed patient population is consistent with the recommendations in the 2007 American Academy of Pediatrics article, Recommendations for Treatment of Child and Adolescent Overweight and Obesity (Spear, et al, 2007), which supports medication use in the 6 to 11 year age group as part of a staged approach (Tertiary Care Intervention in patients with a BMI 99th percentile and at least 1 co-morbidity).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex with a body weight greater than 60 kg

OR

Healthy male or female children, age 9 to 11 years at Screening, with a BMI that is greater than or equal to the US-weighted mean of the 99th percentile based on age and sex, and a body weight greater than 60 kg associated with at least 1 co-morbid weight-related condition (eg, type 2 diabetes mellitus, hypertension, dyslipidemia)

- Type 2 Diabetes as defined by American Diabetes Association Standards of Diabetes Care, 2013.
- Stage 1 primary hypertension (blood pressure in the 95th to 99th percentile plus 5 mmHg for age, sex, and height) as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011) during the Screening Period
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a reduced-calorie diet and an increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension by objective assessments (ie, imaging modality or cardiac catheterization)
4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)
8. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
9. Use of any of the following medications:

a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - linezolid
   - dextromethorphan in any form (eg, OTC cold medicines)
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

b) Others
   - antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
   - oral steroids (topical and inhaled steroids are acceptable)
   - stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
   - benzodiazepines

10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
14. Any use of a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before Screening
17. Known to be human immunodeficiency virus positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology

19. Malignancy within 5 years before Screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
23. Subjects 12 to 17 years old with a BP in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Those subjects over 12 years old who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy 1 time.
24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \bullet 0.5\ H_2O$
- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a

calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by age group (9 to 11 years old and 12 to 17 years old) and sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio. It is planned that at least 30% of the subjects will be enrolled into the 9 to 11 year age group.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs
   - SSRIs
   - SNRIs
   - TCAs
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - MAOIs
   - linezolid
   - dextromethorphan
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

b. Others
   - antiseizure medications including valproic acid, zonisamide, and lamotrigine
   - oral steroids (topical or inhaled steroids are acceptable)
   - stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
   - benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using standard method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for population PK analyses. At Weeks 12, 28, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing. At the Week 36 visit, subjects will take

the morning dose at home, and 1 blood sample for determination of plasma concentration of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Blood samples will be collected to determine lorcaserin plasma exposure and population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and following response to lorcaserin:

- Change from Baseline in BMI
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluations for hematology, thyroid function, adrenal functions, and biochemical blood and urine biomarkers of bone health; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and prolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of children and adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Children and adolescent sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up. Any subject with symptoms or signs of cardiac valvular disease or pulmonary hypertension may be evaluated by local echocardiographic assessment at the discretion of the investigator if deemed medically indicated.

The C-SSRS will be used to assess all children and adolescents in the study for any signal of depression or suicidal ideation or behavior. Additionally, mood will be assessed using the CDI-2 and effects on cognitive function will be assessed using WRAML-2.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS, CDI-2, and WRAML-2 in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin

- Fibroadenomas of the breast or ductal carcinoma in situ

The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects),
Biomarkers of bone health	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other	Albumin, calcium, globulin, glucose, HbA_{1c}, HDL cholesterol, lactate dehydrogenase, LDL cholesterol, phosphorus, total protein, total cholesterol, triglycerides, prolactin, uric acid, urine ß-hCG,
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs,

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated

method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

WRAML-2

The WRAML-2 administration will consist of the Core Battery, which provides scores on Verbal Memory, Visual Memory, and Attention/Concentration. There are 6 subtests (2 for each area). The tests provide standardized scores based on age and gender, and are appropriate for ages 5 to 90 years. The WRAML-2 will be used to assess lorcaserin effects on cognitive function. In addition, signs and symptoms of cognitive related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF.

CDI-2

The CDI-2 is a self-administered depression rating scale for use in children ages 7 to 17 years. It consists of 28 items and provides a total score, scores on 2 scales, and 4 subscales. CDI-2 will be used to assess lorcaserin effect on mood changes.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. It will be performed at Baseline and at study visits as designated in the Schedule of Procedures/Assessments (Table 2).

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will be captured in the eCRF.

Hand X-Ray will be evaluated for any potential negative effect on bone age as designated in the Schedules/Assessments (Table 2). Echocardiograms will be performed on the subjects with signs or symptoms of potential valvular disease or pulmonary hypertension. Echocardiogram confirmed cases of FDA-defined valvulopathy or pulmonary hypertension will be captured by AE eCRF. Neuromuscular sign assessment for serotonin syndrome will be performed as designated in the Schedule of Procedures/Assessments (Table 2) to screen for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common

drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X		X	X
Inclusion/exclusion criteria	X	X												
Physical Examination	X	X				X		X			X	X	X	X
Neuromuscular sign assessment for serotonin syndrome[d]			X			X					X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X		X	X		X		X	X		X	X	X	X
Urine drug and cotinine test	X													
Fasting plasma glucose, Fasting Insulin, HOMA-IR, and HbA_{1c} sampling	X	X				X		X			X			X
T4 and TSH	X							X			X			X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
AM serum cortisol		X									X			
Testosterone, Estradiol	X													
Pregnancy test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X
WRAML-2		X		X				X			X	X		X
CDI-2		X	X	X	X	X	X	X	X	X	X	X		X
Hand x-ray for bone age		X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X
Urine NTX		X						X			X			
PK sample						X		X	X		X			X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	Prerandomization[a]		Randomization										Other	
Period:	Screening		Treatment									Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Prolactin	X							X			X			X
Lifestyle modification counseling[e]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event; AM = morning; CDC = Centers for Disease Control and Prevention; CDI-2 = Children's Depression Inventory 2; C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EOS = End of Study, EOT = End of Treatment, HbA_{1c} = hemoglobin A1c, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PICP = carboxyterminal propeptide of type I procollagen PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone, WRAML-2 = Wide Range Assessment of Memory and Learning-2.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits after Visit 2 except for Weeks 12 and 28 (the window for these visits will be broader at ±14 days). Week is shown unless otherwise indicated.

c: On Weeks 12, 28, and 52, subjects will take the morning dose at the clinic, and 2 blood samples for determination of plasma concentrations of lorcaserin will be taken: predose (within 30 minutes before dosing) and within 1 to 3 hours after dosing (time in which the dose was taken on the night previous to the visit must be recorded). On Week 36, the subjects will take the morning dose at home (time of morning dosing at home must be recorded), and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

d: Accompanied by an abbreviated physical examination for clonus

e: Lifestyle modification counseling will also be performed at Weeks 3, 24, 32, 40, and 48 in addition to counseling at the visits in the schedule of assessments table above.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Visits 2, 3, 4, 6, 8; 11/EOT, EOS	12×8=96
T4, TSH, Cortisol, Testosterone, estradiol, Serum OC and PICP, Hydroxy-proline; Fasting prolactin levels	10	Screening: 1 Visits 8; 11/EOT/Early discontinuation	10×3=30
Prolactin, FPG, Insulin, and HbA_{1c} sampling	4	Screening: 1 Visits 2, 6, 8; 11/EOT/Early discontinuation	4×5=20
PK/PD blood sampling	4	Visits 6, 8, 9, and 11/EOT/Early discontinuation (2 samples each)	8×4=32
Total			178

EOS = End of Study; EOT = End of Treatment; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; OC = osteocalcin; PD = pharmacodynamic; PICP = carboxyterminal propeptide of type I procollagen; PK = pharmacokinetics; T4 = thyroxine; TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the

AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset pulmonary hypertension
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

  The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF:

- Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code

for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has

the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY EFFICACY ENDPOINT

- Change in BMI from Baseline to Week 52

9.7.1.1.2 SECONDARY EFFICACY ENDPOINTS

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change and percentage change in BMI from Baseline to Week 52 and proportion (%) of subjects achieving at least a 5% or 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52

- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of BMI**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the mixed effect model repeated measurement analysis (MMRM) assuming the missing data is missing at random (MAR) with factors of treatment, visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), age group (9 to 11 years old and 12 to 17 years old), sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline BMI as a covariate. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model.

Subgroup analyses and additional sensitivity analyses will be performed as appropriate including multiple imputation methods assuming the missing values are MAR and missing not at random (MNAR) to handle missing data.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Multiple imputation (MI): the same primary efficacy analyses described above will be analyzed using MI for impute the missing data, assuming the missing values are MAR and MNAR.

- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Additional sensitivity analyses may also be explored and described in the SAP, if deemed appropriate.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, age group (9 to 11 years old and 12 to 17 years old) and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

Unless specified, for all other secondary efficacy endpoints, the continuous variables will be analyzed using MMRM and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including age group (9 to 11 years old and 12 to 17 years old), sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Change from Baseline in BMI will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, percentage of BMI change, proportion [%] of patients achieving ≥5% and ≥10% BMI reduction, and change in waist circumference from baseline) will also assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in BMI from baseline and the probability of achieving at least a 5% and at least a 10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values (including biomarkers), ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, suicidal ideation, cognitive function, behavior, and mood will be evaluated by the C-SSRS, WRAML-2, CDI-2, and C-SSRS, respectively, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study

drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and
- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including children and adolescent growth evaluations using CDC growth chart and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, neuromuscular sign assessment for serotonin syndrome, signs and symptoms of priapism and prolactinemia, study drug effect on cognitive function assessed by WRAML-2, assessment of suicidality using C-SSRS, and mood assessment using CDI-2 will be also be summarized by treatment group at each scheduled visit.

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

Appendix 3 Pharmacodynamic and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), and other biomarker analysis. These samples may be used for discovery or validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The pharmacogenetics (PG) samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events (AEs) related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PG, or other biomarker results are obtained that may have clinical relevance, Institutional Review Board review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

SIGNATURES

Authors:

PPD

Date

Neuroscience Business Group

Eisai Inc.

PPD

Date

Eisai Inc.

PPD

Date

Neuroscience Business Group

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes		Throughout
Belviq to Belviq XR	The XR formulation will replace the IR formulation in the United States market to support the ease of administration	Throughout
Patients to Subjects	Corrected per Style Guide	Throughout
Subject population to include children ages 9 to 17 years	Expand the age of the population due to the change of pediatric development strategy A single dose pharmacokinetic study in pediatric obese subjects (APD356-A001-026) indicated that patients with body weight greater than or equal to 60 kg can be administered a dose similar to that given to adults and adolescents. Based on Centers for Disease Control and Prevention (CDC) growth chart data, almost all subjects over 9 years of age are likely to be at or over 60 kg body weight. Therefore, children age 9 to 11 years have been included in the current study.	Title Page Synopsis • Study Protocol Title • Objectives • Study Design • Inclusion Criteria • Assessments • Efficacy Analyses • Safety Analyses Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.2 Section 9.3.2 Section 9.4.3 Section 9.5.1.5 Section 9.5.1.5.1 Section 9.5.2 Section 9.5.1.5.3 Section 9.5.1.5.8 Section 9.7.1.6 Section 9.7.1.8

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Additional safety assessments including cognitive function, serotonin syndrome components, bone health and endocrine function, priapism, and symptoms associated with hyperprolactinemia were added.	Per United States Food and Drug Administration (FDA) request	Synopsis • Efficacy Assessments • Pharmacokinetic Assessments • Safety Assessments Section 9.5.1.3 Section 9.5.1.5 Section 9.5.1.5.8 Section 9.7.1.8 Section 9.7.1.8.1
Change to primary and key secondary endpoints	Per FDA request	Synopsis • Other Secondary Efficacy Endpoints Section 8.1 Section 8.2
Analysis of primary endpoint changed	Per FDA request	Synopsis • Primary Efficacy Analysis Section 9.5.1.3 Section 9.7.1.1.2 Section 9.7.1.6
Update to reporting of study-specific adverse events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.4.3.2
Inserted Section 9.3.3: Removal of Subjects From Therapy or Assessment	Per protocol template	Section 9.3.3
Updated allowed and prohibited prior and concomitant therapies	For clarification	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.6
Update to reporting of adverse events	To provide clearer guidance for the correct reporting of adverse events	Section 9.5.1.5.1 Section 9.5.4.1 Section 9.7.1.8.2

Revision History Previous Version (Original Protocol): v1.0 Current Version (Revision): v2.0 Date of Revisions: 22 Jul 2016		
Change	**Rationale**	**Affected Protocol Section(s)**
Update to Introduction and to Completion/ Discontinuation of Subjects	To provide details of plans to maximize subject retention	Section 7.1 Section 9.5.5

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	v1.0 16 Apr 2015 (original protocol) v2.0 22 Jul 2016 (Revision)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: Belviq XR® (lorcaserin hydrochloride)

Study Protocol Title

A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction With Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States

Study Period and Phase of Development

Approximately 24 months from first subject enrolled to last subject's last visit or last assessment

Phase 4

Objectives

Primary Objective

To demonstrate weight loss efficacy by change in body mass index (BMI) during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) as compared to placebo

Key Secondary Objective

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

Other Secondary Objectives

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
  - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
  - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L] / 405) during 52 weeks of treatment
  - Changes in cardiovascular risk factors associated with obesity (eg, hypertension, dyslipidemia) during 52 weeks of treatment
- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range

Assessment of Memory and Learning-2 (WRAML-2), on mood by Children's Depression Inventory 2 (CDI-2), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by Centers for Disease Control and Prevention (CDC) growth chart, on sexual maturation measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health.

- To assess the pharmacokinetics (PK) of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and body weight and probability of achieving at least a 5% and at least a 10% reduction in BMI and body weight from baseline at Week 52 using population PK/ PD modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese children and adolescents, ages 9 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by age group and sex. At least 30% of the total subjects should be ages 9 to 11 years. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes diet and exercise counseling.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52. The Follow-Up Period will extend from the End of Treatment visit to the End of Study visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex, but is less than 44 kg/m^2

OR

Healthy male or female children, age 9 to 11 years at Screening, with a BMI that is greater than or equal to US-weighted mean of the 99th percentile based on age and sex, but is less than 44 kg/m^2, and a body weight greater than 60 kg associated with at least 1 co-morbid weight-related condition (eg, type 2 diabetes mellitus, hypertension, dyslipidemia)

- Type 2 Diabetes is defined by American Diabetes Association Standards of Diabetes Care, 2013.
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

(Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

2. Subjects and their families not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a reduced-calorie diet and an increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians
   c. No history of Attention Deficit Hyperactivity Disorder, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension (PH) by objective assessments (ie, imaging modality or cardiac catheterization)
4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, known genetic causes of obesity)
8. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
9. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine

oxidase inhibitors (MAOIs) within 30 days before Randomization, including:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- bupropion
- triptans
- St. John's Wort
- tryptophan
- linezolid
- dextromethorphan in any form (eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others

- antiseizure medications including valproic acid, zonisamide, topiramate, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine, and Dexedrine)
- benzodiazepines

10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening
14. Adherence to a very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before Screening
17. Known to be human immunodeficiency virus positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology
19. Malignancy within 5 years before Screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay,

pervasive development disorders, autism)

22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
23. Uncontrolled hypertension, defined as blood pressure (BP) in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy one time.
24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation
    c. Are using hormonal contraceptives, but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

29. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

Study Treatment(s)

Test drug

Belviq XR (lorcaserin hydrochloride) will be provided as orange-colored, round, film-coated,

biconvex tablets with one 20-mg tablet administered orally QD.

Comparator Drug

Matching placebo, 1 tablet administered orally QD

Duration of Treatment

Prerandomization Phase: 30 days

Randomization Phase: 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents or other agents in combination with Belviq XR are prohibited:

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort
- tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications including valproic acid, zonisamide, and lamotrigine
- oral steroids (topical and inhaled steroids are acceptable)
- stimulant medications (eg, Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be measured to calculate BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting

plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and Homeostasis Model Assessment (HOMA) IR to assess cardiovascular and metabolic risk profiles from Baseline to Week 52

- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Pharmacokinetic Assessments

Plasma lorcaserin concentrations will be measured at Weeks 12, 28, 36, and 52 for analysis of population PK. At Weeks 12, 28, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing. At the Week 36 visit, subjects will take the morning dose at home, and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

Pharmacodynamic Assessments

- Change from baseline in BMI and body weight
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI and body weight

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluation for hematology, thyroid function, adrenal function and biochemical blood and urine biomarkers of bone health; blood chemistry and urine values; neuropsychiatric events; periodic measurement of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs or symptoms of priapism and prolactinemia; and performance of physical examinations. In patients with potential prolactin-related AEs, such as galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of children and adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination, at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Children and adolescent sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up. Any subject with symptoms or signs of cardiac valvular disease or PH will be further evaluated by centralized echocardiogram assessments. The assessments will be adjudicated and be followed up by echocardiogram assessments at end of the study. The events of confirmed United States Food and Drug Administration (FDA) defined valvulopathy and PH will be captured in AE electronic Case Report Form (eCRF).

The (C-SSRS) will be used to assess all children and adolescents in the study for any signal of

depression or suicidal ideation or behavior. Additionally, mood will be assessed using the CDI-2 and effects on cognitive function will be assessed using WRAML-2.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography method coupled with tandem mass spectrometry.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- Change in BMI from Baseline to Week 52

Key Secondary Efficacy Endpoint

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

Other Secondary Efficacy Endpoints

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 post dose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and a list of major protocol violations will be included in the statistical analysis plan (SAP) and finalized before data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD

parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of body weight.

Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, and the PP will be used as a supportive analysis. Unless otherwise specified, a 2-sided α=0.05 significance level will be used in all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the mixed effect model repeated measurement analysis (MMRM) with factors of treatment visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), age group (9 to 11 years old and 12 to 17 years old), sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline BMI as a covariate. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model.

Subgroup analyses and additional sensitivity analyses will be performed as appropriate including multiple imputation methods assuming the missing values are missing at random (MAR) and missing not at random (MNAR) to handle missing data.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Multiple imputation (MI): the same primary efficacy analyses described above will be analyzed using MI for impute the missing data, assuming the missing values are MAR and MNAR.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Additional sensitivity analyses may also be explored and described in the SAP, if deemed appropriate.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, age group (9 to 11 years old and 12 to 17 years old), sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

In general, for all other secondary efficacy endpoints, the continuous variables will be analyzed using MMRM and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including age group (9 to 11 years old and 12 to 17 years old), sex (male and female), and race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates such as baseline characteristics or demographics on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Probability of achieving at least a 5% and at least a 10% body weight reduction and change from Baseline in body weight will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, BMI change, percentage of BMI change, proportion [%] of patients achieving ≥10% BMI reduction, and change in waist circumference from baseline) will also assessed as part of the PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in body weight from baseline and the probability of achieving at least a 5% and at least a 10% change in body weight from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values (including biomarkers), ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, suicidal ideation,

cognitive function, behavior, and mood will be evaluated by the C-SSRS, WRAML-2, CDI-2, and C-SSRS, respectively, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

Interim Analyses

Not applicable

Sample Size Rationale

The proposed sample size is based on the comparison of the primary efficacy endpoint, change in BMI from Baseline to Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and the placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero to infinity
BID	twice per day
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CDI-2	Children's Depression Inventory 2
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LNH	low/normal/high
IxRS	interactive voice or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MAR	missing at random
MI	multiple imputation
MMRM	mixed effect model repeated measurement analysis
MNAR	missing not at random
NTX	N-telopeptide
OC	osteocalcin
OTC	over-the-counter
PD	pharmacodynamic(s)
PG	pharmacogenetic(s)
PH	pulmonary hypertension
PI	principal investigator
PICP	carboxyterminal propeptide of type I procollagen
PK	pharmacokinetic(s)
PP	Per Protocol Analysis Set
PT	preferred term
QD	once daily
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SMD	standardized mean difference
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T4	thyroxine
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell
WRAML-2	Wide Range Assessment of Memory and Learning-2

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [21 CFR] Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination or a temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity

Obesity has become a global epidemic in western civilization, causing a serious public health concern. In the United States, the prevalence of obesity in adolescents ages 12 and 19 years has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). The prevalence of obesity in children in United States is also high. The United States Centers for Disease Control and Prevention (CDC) reported in 2012 that 17.7% of children ages 6 to 11 years are obese. Obesity in children and adolescents, defined in the United States as greater than or equal to the 95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the United States and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and the West Pacific, prevalence of obesity in these countries has also increased significantly, at a rate comparable to that in the United States.

Childhood and adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the 1st time in 200 years (Peeters , et al, 2003).

As a result, there is a significant impact on the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately $14 billion per year in the United States (Trasande and Chatterjee, 2009). Obesity-related medical costs in general are expected to rise significantly because today's obese children are likely to become tomorrow's obese adults.

Current approaches to weight management include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs, and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise.

The current standard of care for treatment of obesity in pediatric subjects ranges from lifestyle intervention in children less than 8 years of age to use of pharmacotherapy in adolescents over 12 years of age (McGovern, et al, 2008; Spear, et al, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age. However, it is associated with gastrointestinal side effects (Xenical PI. 2015), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI above the 97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine, et al, 2005).

Obtaining maximum retention in the study is a major goal in order to minimize missing data. A number of strategies have been used in prior adolescent weight loss studies that will be used in the present study to help retain participants. These include a highly trained and competent staff, ample waiting area, readily available parking (at no cost), access to mass transit, and reminder and follow-up calls. In addition, we will provide fun and interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. Families will receive a reimbursement of $30 per family for assessments completed at Baseline and Month 6, and $100 at Month 12. Further, we will make home visits for assessments for families, as needed, to maximize data collection. We anticipate achieving a 75% or greater retention rate at Month 12. By using these retention strategies, we hope that we will maximize participant retention, which will help us cope with missing data.

7.1.1 APD356/Belviq (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

Belviq is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 Jun 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of at least 30 kg/m^2 (obese), or adult patients with a BMI greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/Belviq (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of Belviq in studies of more than 7700 adult subjects, including 604 subjects with Type 2 diabetes mellitus, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the Belviq dose met the following prespecified endpoints:

- A significantly greater proportion of adult subjects taking Belviq 10 mg twice per day (BID) (47%) lost at least 5% of baseline body weight at 52 weeks as compared to subjects taking placebo (23%). A significantly greater proportion of subjects taking Belviq 10 mg BID (22.4%) lost at least 10% of baseline body weight at 1 year as compared to subjects taking placebo (8.7%).
- The mean weight loss at 1 year in adult subjects taking Belviq 10 mg BID (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

An integrated evaluation of the data from the pediatric, adolescent, and adult subjects revealed that the relationship between lorcaserin area under the curve (AUC) and body weight in pediatric and adult subjects is consistent irrespective of the individual studies or age range of the study population. Irrespective of age, lorcaserin AUC values in the pediatric subjects with body weight of greater than 60 kg overlapped with the data observed from the studies involving adult subjects, suggesting a fixed dose approach similar to adults can be used for children and adolescent subjects with body weight greater than 60 kg.

In preadolescent and adolescent obese populations, it is anticipated that Belviq XR will result in similar effects. As part of FDA postmarketing requirements, this study is designed to characterize the efficacy and safety of Belviq XR in adolescent obese populations in the United States, as well as in children ages 9 to 11 years. It is also intended to support an indication for chronic weight management for obese children and adolescents ages 9 to 17 years. Thirty percent of the subjects 9 to 11 years of age from this study will be stratified and added to the 50 subjects 6 to 8 years of age in the open label pharmacokinetic (PK) only cohort in the APD356-404 study to be used to support a safety population (n=110) in the open label study designed for obese subjects 6 to 8 years of age using partial extrapolation with PK for efficacy.

7.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product for children and adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant.
- The proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose at least 5% of baseline body weight, and the difference between groups is statistically significant.

FDA awarded a weight management indication for Belviq based on Phase 3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking Belviq (47%) lost at least 5% of baseline body weight at 1 year as compared to subjects taking a placebo (23%). It is anticipated that a similar effect will be demonstrated in older children (9 to 11 years of age) and obese adolescents, where weight

loss will be assessed using BMI measurements to account for growth. In this study, the objective is to demonstrate that BMI reduction will be achieved during 52 weeks of treatment with Belviq XR 20 mg administered once daily (QD) compared to placebo in obese children and adolescents.

In the Phase 3 orlistat study in obese adolescents and children mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of the subjects achieved a 5% or greater BMI reduction compared to 15.7% in the placebo group. The placebo-corrected BMI reduction was about 0.86 kg/m^2.

There are limited trials for weight reduction in the adolescent population, ages 12 to 17 years, and none in children under the age of 9 years (Peirson, et al, 2015). Thirty-one studies (29 behavioral, 2 pharmacological and behavioral) were included in a meta-analysis of randomized studies conducted in primary care centers in overweight and obese children and youth ages 2 to 18 years using behavioral (diet, exercise, and lifestyle) and pharmacological interventions and providing 6-month postbaseline BMI or prevalence of overweight or obesity. Both interventions showed a significant effect on BMI in favor of treatment (behavioral: standardized mean difference [SMD] -0.54, 95% confidence interval [CI] -0.73, -0.36; orlistat plus behavioral: SMD -0.43, 95% CI -0.60, -0.25). The studies reported no significant difference between groups in the likelihood of reduced prevalence of overweight or overweight and obese. A great deal of variation was noted across efficacious interventions. In conclusion, this meta-analysis demonstrated low-quality evidence that behavioral treatments alone are associated with a smaller effect in terms of reduced BMI compared with the effect shown by combined behavioral and pharmacological interventions. This may be because the effect size in the randomized, double blind, placebo controlled, phase 3 orlistat study in adolescents was relatively low and there was a lack of maintenance effect. These subjects started to regain their BMI after 6 months of treatment. At end of the study, only 26.5% of subjects achieved a 5% or greater BMI reduction compared to 15.7% in placebo group. In a sibutramine Phase 3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least a 5% BMI reduction compared to 21% of subjects in the placebo group. In addition, sibutramine resulted in a substantial reduction in mean BMI (between-group difference, 2.9 kg/m^2) and mean weight (between-group difference, 8.4 kg) compared to placebo (Berkowitz, et al, 2006). Unlike the weight loss effect of Belviq in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment.

In this proposed study, it is assumed that treatment with Belviq XR 20 mg will lead to a BMI reduction of more than 1 kg/m^2, and a higher proportion of subjects will achieve more than a 5% and 10% BMI reduction compared to placebo. A between-group difference of 24% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, et al, 2005; Berkowitz, et al, 2006) and other metabolic or dyslipidemia medication products (ezetimibe, simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

To demonstrate weight loss efficacy by change in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

8.2 Secondary Objectives

KEY SECONDARY OBJECTIVE

To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a at least a 5% reduction in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD as compared to placebo

OTHER SECONDARY OBJECTIVES

- To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with at least a 5% reduction in BMI after an initial 12 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate weight loss efficacy by percentage change from baseline in BMI during 52 weeks of treatment with Belviq XR 20 mg administered QD compared to placebo
- To demonstrate the efficacy of treatment with Belviq XR 20 mg QD by assessing:
    - Other weight loss effects (eg, proportion [%] of subjects achieving at least a 10% BMI reduction, change in waist circumference) at the end of 52 weeks of treatment
    - Effects on glycemia, insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; glucose [mg/dL] × insulin [mU/L] / 405) during 52 weeks of treatment
    - Changes in cardiovascular risk factors associated with obesity (eg hypertension, dyslipidemia) during 52 weeks of treatment

- To assess the safety of Belviq XR, including the effects on cognitive function by Wide Range Assessment of Memory and Learning-2 (WRAML-2), on mood by Children's Depression Inventory 2 (CDI-2), on signal of suicidal ideation or behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS), on growth measured by CDC growth chart, on sexual maturation measured by Tanner Staging scores, and on other growth and development parameters by measuring sex hormones, thyroid function, adrenal function, bone age, and biochemical markers of bone health.
- To assess the PK of lorcaserin using population PK modeling
- To assess relationships between plasma exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and

body weight and probability of achieving at least a 5% and at least a 10% reduction in BMI and body weight from baseline at Week 52 using population PK/ PD modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese children and adolescents ages 9 to 17 years. Approximately 360 subjects will be randomized in a 1:1 ratio to Belviq XR 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will be stratified by age group and sex. At least 30% of total subjects should be ages 9 to 11 years for the reasons outlined above in Section 7.1.1.2. Subjects will receive Belviq XR 20 mg or placebo QD in a 1:1 ratio for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-Up Period will extend from the End of Treatment (EOT) visit to the End of Study (EOS) visit.

Subjects who screen fail can be re-screened only once after 60 days. All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization/Pretreatment Phase

Screening will occur during the Prerandomization Phase at Visit 1

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and assent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Careful initial screening is important in the recruitment of families who both fully understand the requirements of this 1 year, randomized, controlled trial and are truly interested in participation. Interested caregivers and adolescents will be screened by phone to assess preliminary entry criteria. Candidates will be given a brief description of the program and general study requirements, with an adolescent and a caregiver who is willing to participate. If preliminary entry criteria are met, adolescents and their caregivers will be invited to an initial in-clinic meeting to further discuss the study. A complete description of the study including assessments, the number of visits, the lifestyle program, the fact that the adolescent would be taking either the study drug or a placebo, the duration of the study, and the necessity of having an adolescent wishing to participate as well as a participating caregiver will be described. Consent and assent will be obtained and copies of the signed forms will be provided to families. The importance of the study and its scientific merit will be discussed. Ineligible adolescents will be referred to local weight management resources. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization/Treatment Phase

The Randomization Phase will consist of 2 periods: the Treatment Period and the Follow-Up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency of Belviq XR in this study is 20 mg QD. The PK parameters of a single 10-mg dose of Belviq were evaluated in healthy, adolescent obese subjects in Study APD356-025 and healthy, obese pediatric subjects ages 6 to 11 years in Study APD356-A001-026. Overall, the PK parameters of Belviq and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of Belviq 10 mg to a total of 8 healthy adolescent (age 12 to 17 years) obese subjects, the mean maximum concentration observed and the area under the concentration-time curve from time zero to infinity ($AUC_{(0\text{-inf})}$) were 36.5 ng/mL and 464 hr×ng/mL, respectively. The mean Belviq terminal phase half-life was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (QD) in adolescent subjects.

Additionally, a single dose PK study in 8 healthy obese pediatric subjects ages 6 to 11 years of age was recently completed. The PK analysis after a single 10-mg dose of lorcaserin revealed that the lorcaserin $AUC_{(0\text{-inf})}$ values tended to increase with decreasing body weight and age. However, the body weight normalized $AUC_{(0\text{-inf})}$ values were similar across the age groups, therefore the data indicated no effect of age on the lorcaserin PK. Integrated assessment of the PK versus body weight relationship, pooling the data from pediatric and adult subjects from previous studies, suggested that the lorcaserin area under the curve values for subjects with body weight of at least 60 kg overlapped with the area under the curve values from adolescents and adults. Therefore, no dose adjustment relative to adults and adolescents is deemed necessary for pediatric subjects with a body weight of at least 60 kg.

Based on CDC growth charts, the likelihood of enrolling subjects who are younger than 9 years of age with body weight of at least 60 kg is low; therefore, the current study is designed to enroll the subjects between 9 to 17 years of age.

The targeted study population comprises 360 obese children and adolescents 9 to 17 years of age.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI in or above the 95th percentile (Barlow, 2007). Obesity in children will be identified using gender- and age-specific BMI measurement. Obesity in children (9 to 11 years of age) is defined by The American Academy of Pediatrics 2007 recommendation as BMI in the 99th percentile and at least 1 co-morbidity (Spear, et al, 2007).

The proposed patient population is consistent with the recommendations in the 2007 American Academy of Pediatrics article, Recommendations for Treatment of Child and Adolescent Overweight and Obesity (Spear, et al, 2007), which supports medication use in the 6 to 11 year age group as part of a staged approach (Tertiary Care Intervention in patients with a BMI 99th percentile and at least 1 co-morbidity). Although we acknowledge that recommendations are not necessarily different for the older children and adolescents in this publication, utilizing broader inclusion criteria in the 12 to 17 year age group allows for more generalizability, whereas the more stringent approach in the 6 to 11 year age group better balances potential benefits with some of the uncertainties of treatment in this age group.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics, baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug. Subjects who screen fail can be re-screened only once after 60 days.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy male or female adolescents, age 12 to 17 years at Screening, with a BMI that is greater than or equal to the United States (US)-weighted mean of the 95th percentile based on age and sex, but is less than 44 kg/m^2

OR

Healthy male or female children, age 9 to 11 years at Screening, with a BMI that is greater than or equal to the US-weighted mean of the 99th percentile based on age and sex, but is less than 44 kg/m^2, and a body weight greater than 60 kg associated with at least 1 co-morbid weight-related condition (eg, type 2 diabetes mellitus, hypertension, dyslipidemia)

- Type 2 Diabetes is defined by American Diabetes Association Standards of Diabetes Care, 2013.
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

2. Subjects and their families are not planning to move away from the area for the duration of the study
3. Subjects able and willing to comply with all aspects of the study, including a reduced-calorie diet and an increased physical activity program
4. Subjects considered in stable health in the opinion of the investigator
5. Caregivers or guardians meet the following requirements:
   a. Able and willing to support and supervise study participation in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
   b. Able and willing to personally comply with and execute all aspects of the study requirements for the caregivers or guardians
   c. No history of Attention Deficit Hyperactivity Disorder, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements or significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension (PH) by objective assessments (ie, imaging modality or cardiac catheterization)
4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease as evidenced by a serum creatinine greater than 1.5×upper limit of normal (ULN), serum transaminases greater than 3×ULN, or total bilirubin greater than 1.5×ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia within 2 years before Screening, Attention Deficit Hyperactivity Disorder, any Diagnostic and Statistical Manual of Mental Disorders, 5th Edition depressive disorder, suicidal ideation or behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (eg Prader-Willi syndrome, Bardet Biedl syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for

longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)

8. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
9. Use of any of the following medications:
   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors (MAOIs) within 30 days before Randomization, including:
      - selective serotonin reuptake inhibitors (SSRIs)
      - serotonin norepinephrine reuptake inhibitors (SNRIs)
      - tricyclic antidepressants (TCAs)
      - bupropion
      - triptans
      - St. John's Wort
      - tryptophan
      - linezolid
      - dextromethorphan in any form (eg, OTC cold medicines)
      - lithium
      - tramadol
      - antipsychotics or other dopamine antagonists
   b) Others
      - antiseizure medications including valproic acid, zonisamide, topiramate and lamotrigine
      - oral steroids (topical and inhaled steroids are acceptable)
      - stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
      - benzodiazepines
10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy; cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or impaired glucose tolerance), Type 2 diabetes treated with oral anti-diabetic agents (excluding sulfonylurea) or non-insulin injectable antidiabetic agents, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of Belviq XR within 6 months before Screening or hypersensitivity to Belviq XR or any of the excipients
13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of more than 5 kg within 3 months before Screening

14. Adherence to a of very-low-calorie (<1000 calories/day) weight loss diet within 6 months before Screening
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before Screening
17. Known to be human immunodeficiency virus positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology
19. Malignancy within 5 years before Screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a caregiver or guardian to supervise study participation
21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <70], moderate to severe cognitive developmental delay, pervasive development disorders, autism)
22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening or any time between screening and randomization
23. Uncontrolled hypertension, defined as blood pressure (BP) in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days. Subjects who had uncontrolled hypertension at Screening can be rescreened more than 1 month after initiation or adjustment of antihypertensive therapy one time.
24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator, including consideration of any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Female subjects who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive β-human chorionic gonadotropin test). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Female subjects of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation

c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation

(NOTE: All female subjects will be considered to be of childbearing potential unless they have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

29. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of Belviq XR 20 mg or placebo orally QD.

Belviq XR (lorcaserin hydrochloride) is a Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C–IV) approved by the FDA.

Belviq XR will be provided as orange-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). Belviq XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of Belviq XR

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \bullet 0.5\ H_2O$

- Molecular weight: 246.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit or carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III to V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Subjects will be centrally stratified by age group (9 to 11 years old and 12 to 17 years old) and sex (male and female). Within each stratum, subjects will be randomized to receive either Belviq XR 20 mg or placebo QD in a 1:1 ratio. It is planned that at least 30% of the subjects will be enrolled into the 9 to 11 year age group.

Randomization will be performed centrally by an interactive voice or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-Up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication Case Report Form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped. Any of the following serotonergic agents in combination with Belviq XR is prohibited:

a. Serotonergic drugs
   - SSRIs
   - SNRIs
   - TCAs
   - bupropion
   - triptans
   - St. John's Wort
   - tryptophan
   - MAOIs
   - linezolid
   - dextromethorphan
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

b. Others
   - antiseizure medications including valproic acid, zonisamide, and lamotrigine

- oral steroids (topical or inhaled steroids are acceptable)
- stimulant medications (Ritalin, Concerta, Biphetamine and Dexedrine)
- benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Per visit schedule, subjects will return unused study drug and be given a new supply; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate-Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.3 Efficacy Assessments

- Body weight and height will be measured using standard method (Lohman T, et al, 1988) to calculate changes in BMI; BMI will then be used to calculate the proportion (%) of patients achieving at least a 5% and at least a 10% BMI reduction.
- Measurement of systolic and diastolic BP, heart rate, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), and HOMA-IR to assess changes in cardiovascular and metabolic risk profiles from Baseline to Week 52
- Prehypertension and primary hypertension as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)
- Dyslipidemia as defined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for population PK analyses. At Weeks 12, 28, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of

plasma concentrations of lorcaserin will be taken at each of these visits: within 30 minutes before dosing and within 1 to 3 hours after dosing. At the Week 36 visit, subjects will take the morning dose at home, and 1 blood sample for determination of plasma concentration of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

- Change from Baseline in BMI and body weight
- Proportion (%) of patients achieving at least a 5% and at least a 10% reduction in BMI and body weight

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with lorcaserin plasma exposure.

9.5.1.4.3 PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); electrocardiograms (ECGs); laboratory evaluations for hematology, thyroid function, adrenal functions, and biochemical blood and urine biomarkers of bone health; blood chemistry and urine values; neuropsychiatric events; periodic measurements of vital signs, neuromuscular signs for screening potential serotonin syndrome, and signs and symptoms of priapism and prolactinemia; and performance of physical examinations. In subjects with potential prolactin-related AEs, such galactorrhea, changes in libido, or changes to menstrual cycle, prolactin level will be measured and assessed. Study drug effect on growth of children and adolescents will be evaluated using the CDC growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-Up; a full physical examination at Baseline, Weeks 12, 28, 52, and at Follow-Up; and bone age determination by x-ray of the hand at Baseline, Weeks 12, 28, and 52. Children and adolescent sexual maturation will be evaluated by assessing sex hormones and self-reported changes in Tanner Staging at Baseline, Weeks 28 and 52, and at Follow-Up. Any subject with symptoms or signs of cardiac valvular disease or PH will be further evaluated by centralized echocardiogram assessments. The assessments will be adjudicated and be followed up by echocardiogram assessments at end of the study. The events of confirmed FDA defined valvulopathy and PH will be captured in the AE electronic case report form (eCRF).

The C-SSRS will be used to assess all children and adolescents in the study for any signal of depression or suicidal ideation or behavior. Additionally, mood will be assessed using the CDI-2 and effects on cognitive function will be assessed using WRAML-2.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is Belviq XR (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [QTc]) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS, CDI-2, and WRAML-2 in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least 1 of the following: Spontaneous clonus; Inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior
- Priapism
- New onset valvular heart disease
- New onset PH
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function	T4, TSH
Adrenal function	Cortisol
Sex hormones	Testosterone (male subjects), estradiol (female subjects),
Biomarkers of bone health	Serum OC and PICP, Hydroxy-proline; Urine NTX
Prolactin	Fasting prolactin levels
Other	Albumin, calcium, globulin, glucose, HbA_{1c}, HDL cholesterol, lactate dehydrogenase, LDL cholesterol, phosphorus, total protein, total cholesterol, triglycerides, prolactin, uric acid, urine ß-hCG,
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs,

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, OC = osteocalcin; NTX = N-telopeptide, PICP = carboxyterminal propeptide of type I procollagen; RBC = red blood cell, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated

method. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

WRAML-2

The WRAML-2 administration will consist of the Core Battery, which provides scores on Verbal Memory, Visual Memory, and Attention/Concentration. There are 6 subtests (2 for each area). The tests provide standardized scores based on age and gender, and are appropriate for ages 5 to 90 years. The WRAML-2 will be used to assess lorcaserin effects on cognitive function. In addition, signs and symptoms of cognitive related AEs, including impairments in attention, memory, and adverse effects on schoolwork will be captured in the eCRF.

CDI-2

The CDI-2 is a self-administered depression rating scale for use in children ages 7 to 17 years. It consists of 28 items and provides a total score, scores on 2 scales, and 4 subscales. CDI-2 will be used to assess lorcaserin effect on mood changes.

C-SSRS

The C-SSRS collects information pertinent to suicidal ideation and actions. It consists of a Baseline version which will be administered at baseline and a Since Last Visit version which will be administered at the remaining visits. C-SSRS will be used to assess signal of depression and suicidal ideation or behavior. It will be performed at Baseline and at study visits as designated in the Schedule of Procedures/Assessments (Table 2).

Signs and symptoms of priapism (painful erection) and hyperprolactinemia (menstrual cycle abnormalities or galactorrhea) will be captured in the eCRF.

Hand X-Ray will be evaluated for any potential negative effect on bone age as designated in the Schedules/Assessments (Table 2). Echocardiograms will be performed on the subjects with signs or symptoms of potential valvular disease or PH. Echocardiogram confirmed cases of FDA-defined valvulopathy or PH will be captured by AE eCRF. Neuromuscular sign assessment for serotonin syndrome will be performed as designated in the Schedule of Procedures/Assessments (Table 2) to screen for potential serotonergic syndrome components. Serotonergic syndromes that meet the diagnostic criteria will be captured by AE eCRF.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test in female subjects will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common

drugs of use/abuse (eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-Up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]**:**		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X													
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X		X	X
Inclusion/exclusion criteria	X	X												
Physical Examination	X	X				X		X			X	X	X	X
Neuromuscular sign assessment for serotonin syndrome[d]			X			X					X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X		X		X		X	X		X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X		X	X		X		X	X		X	X	X	X
FPG, Fasting Insulin, HOMA-IR and HbA_{1c} sampling	X					X		X			X			X
T4 and TSH	X							X			X			X
AM serum cortisol		X									X			

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	Prerandomization[a]		Randomization										Other	
Period:	Screening		Treatment									Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Testosterone, Estradiol	X													
Fasting Plasma Glucose		X												
HOMA-IR		X												
Fasting Insulin		X												
Pregnancy test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization		X												
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDC growth chart	X	X		X		X		X	X		X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X
WRAML-2		X		X				X			X	X		X
CDI-2		X	X	X	X	X	X	X	X	X	X	X		X
Hand x-ray for bone age		X				X		X			X			X
OC, PICP, and Hydroxy-proline		X						X			X			X

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	Prerandomization[a]		Randomization										Other	
Period:	Screening		Treatment									Follow-Up		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Urine NTX		X						X			X			
PK sample						X		X	X		X			X
Prolactin	X							X			X			X
Lifestyle modification counseling[e]		X	X	X	X	X	X	X	X	X			X	

AE = adverse event; AM = morning; CDC = Centers for Disease Control and Prevention; CDI-2 = Children's Depression Inventory 2; C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EOS = End of Study, EOT = End of Treatment, FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A1c, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; IxRS = interactive voice or web response system, NTX = N-telopeptide, OC = osteocalcin; PICP = carboxyterminal propeptide of type I procollagen PK = pharmacokinetics, T4 = thyroxine, TSH = thyroid stimulating hormone, WRAML-2 = Wide Range Assessment of Memory and Learning-2.

a: Baseline measurements will be collected on Day 1, before drug administration unless specified otherwise.

b: Window ±7 days for all visits after Visit 2 except for Weeks 12 and 28 (the window for these visits will be broader at ±14 days). Week is shown unless otherwise indicated.

c: On Weeks 12, 28, and 52, subjects will take the morning dose at the clinic, and 2 blood samples for determination of plasma concentrations of lorcaserin will be taken: predose (within 30 minutes before dosing) and within 1 to 3 hours after dosing (time in which the dose was taken on the night previous to the visit must be recorded). On Week 36, the subjects will take the morning dose at home (time of morning dosing at home must be recorded), and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours after dosing.

d: Accompanied by an abbreviated physical examination for clonus

e: Lifestyle modification counseling will also be performed at Weeks 3, 24, 32, 40, and 48 in addition to counseling at the visits in the schedule of assessments table above.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Visits 2, 3, 4, 6, 8; 11/EOT, EOS	12×8=96
T4, TSH, Cortisol, Testosterone, estradiol, Serum OC and PICP, Hydroxy-proline; Fasting prolactin levels	10	Screening: 1 Visits 8; 11/EOT/Early discontinuation	10×4=40
Prolactin, FPG, Insulin, and HbA_{1c} sampling	4	Screening: 1 Visits 6, 8; 11/EOT/Early discontinuation	4×5=20
PK/PD blood sampling	4	Visits 6, 8, 9, and 11/EOT/Early discontinuation (2 samples each)	8×4=32
Total			188

EOS = End of Study; EOT = End of Treatment; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; OC = osteocalcin; PD = pharmacodynamic; PICP = carboxyterminal propeptide of type I procollagen; PK = pharmacokinetics; T4 = thyroxine; TSH = thyroid stimulating hormone.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the

AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (listed below) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

- Serotonin syndrome Must have at least 1 of the following: spontaneous clonus; inducible clonus plus agitation or diaphoresis; Ocular clonus plus agitation or diaphoresis; Tremor plus hyperreflexia; Hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus
- Psychosis
- Suicidal behavior
- Priapism
- New onset of valvular heart disease
- New onset PH
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ
- The following additional study specific AE of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as nonserious on the Adverse Event CRF: Suicidal ideation
- Euphoria

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code

for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52 week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Detailed retention strategies will be developed and included in study manual. These include a highly trained and competent staff, easy access to the clinic, reminder and follow-up calls, interactive group sessions with games and hands-on nutrition and physical activity demonstrations, random raffle drawings, social events, birthday and holiday cards, and newsletters. In addition, home visits for assessments of families will be an option, as needed, to maximize data collection. This detailed retention plan will help prevent missing data.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF. The DEA Registrant has the responsibility to comply with local, state, and Federal laws to notify the Field Division Office of the DEA of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 **PRIMARY EFFICACY ENDPOINT**

- Change in BMI from Baseline to Week 52

9.7.1.1.2 **SECONDARY EFFICACY ENDPOINTS**

KEY SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 52

OTHER SECONDARY ENDPOINT

- Proportion (%) of subjects achieving at least a 5% BMI reduction at Week 12
- Proportion (%) of subjects achieving at least a 10% BMI reduction at Week 52
- Percentage change in BMI from Baseline to Week 52
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR from Baseline to Week 52
- Change in BP (systolic and diastolic) and heart rate from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion (%) of subjects with prehypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of all randomized subjects regardless of adherence to study drug.

- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, have no violations of inclusion or exclusion criteria, and have BMI data at Baseline and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized before data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.

- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of body weight**.**

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis Sets will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized for the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary analysis set for all efficacy analyses, while the PP will be used as a supportive analysis. Unless specified otherwise, a 2-sided α=0.05 significance level will be used for all efficacy analyses.

Primary Efficacy Analysis

The primary efficacy endpoint is the change in BMI from Baseline to Week 52. The change from baseline in BMI will be analyzed using the mixed effect model repeated measurement analysis (MMRM) with factors of treatment, visits (Baseline, Week 1, 5, 8, 12, 20, 28, 36, 44, and 52), age group (9 to 11 years old and 12 to 17 years old), sex (male and female), treatment-by-visit interaction as fixed effect, subjects as random effect, and the baseline BMI as a covariate. The unstructured covariance matrix will be used in the analysis and the treatment comparison at Week 52 will be the event of interest. In case of a convergence issue, the Toeplitz covariance structure will be used in the model.

Subgroup analyses and additional sensitivity analyses will be performed as appropriate including multiple imputation methods assuming the missing values are missing at random (MAR) and missing not at random (MNAR) to handle missing data.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP.
- Multiple imputation (MI): the same primary efficacy analyses described above will be analyzed using MI for impute the missing data, assuming the missing values are MAR and MNAR.
- Change from baseline in standardized BMI score (Z-score): The same primary efficacy analyses described above will be repeated using Z-score.

Additional sensitivity analyses may also be explored and described in the SAP, if deemed appropriate.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of subjects achieving at least a 5% BMI reduction at Week 52. The secondary efficacy endpoint will be analyzed only if the test for the primary efficacy endpoint is statistically significant.

The proportion of subjects achieving at least a 5% BMI reduction at Week 52 will be analyzed using a logistic regression model with factors of treatment, age group (9 to 11 years old and 12 to 17 years old) and sex (male and female), and baseline BMI as a covariate using FAS. Subjects with any missing assessment at Week 52 will be considered as treatment failures in this analysis.

Other Secondary Efficacy Analyses

In general, for all other secondary efficacy endpoints, the continuous variables will be analyzed using MMRM and categorical variables will be analyzed using the Cochran Mantel Haenszel test, Chi-square test, or logistic regression as appropriate. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in SAP.

Subgroup analyses will be performed on the primary efficacy endpoint, including age group (9 to 11 years old and 12 to 17 years old), sex (male and female), race (white, black, Asian, and other). Additional subgroups may be explored, if deemed necessary.

No adjustment for multiplicity is planned for other secondary endpoints, subgroup, and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics or demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration and the area under the concentration-time curve from time 0 to 24 hours at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Probability of achieving at least a 5% and at least a 10% body weight reduction change from Baseline will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (eg, BMI change, percentage of BMI change, proportion [%] of patients achieving ≥10% BMI reduction, and change in waist circumference from baseline) will also assessed as PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between lorcaserin plasma exposure and response, including but not limited to change in body weight from baseline and the probability of achieving at least a 5% and at least a 10% change in body weight from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically, depending on the data at the end of study. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety assessments including the incidence of AEs (including changes from baseline in physical examination), growth (CDC growth chart and bone age determined by x-ray of the hand), sexual maturation (Tanner Staging), out-of-normal-range laboratory safety test values, change from baseline in laboratory safety test values (including biomarkers), ECGs, and vital sign measurements will be summarized by treatment group using descriptive statistics or frequency count as appropriate. In addition, suicidal ideation, cognitive function, behavior, and mood will be evaluated by the C-SSRS, WRAML-2, CDI-2, and C-SSRS, respectively, and will also be summarized by treatment group using descriptive statistics or frequency count as appropriate. All WRAML-2 raw scores from the Core Battery will be converted to age and gender standard scores for purposes of intra individual comparisons

No hypothesis testing will be performed for the safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive Belviq XR 20 mg or placebo QD for up to 52 weeks. The extent of exposure will be characterized by duration of exposure (in weeks) for each treatment group.

Duration of exposure will be defined as the number of weeks between the date the subject received the 1st dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 28 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 28 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The following summaries will be reported for TEAES:

- Incidence of TEAEs in descending order of frequency
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT and maximum severity (mild, moderate, or severe)
- Incidence of treatment-related TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- Incidence of TEAEs by SOC, PT, and relationship to study drug (Yes [related] or No [not related])

A subject will be counted only once within a SOC or PT, if the subject experienced more than 1 TEAE within a specified SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs.

- Incidence of TEAEs leading to death
- Incidence of treatment-emergent SAE by SOC and PT
- Incidence of treatment-related treatment-emergent SAE by SOC and PT

In addition, subjects with TEAEs leading to discontinuation from study drug and AEs of special interest as described in Section 9.5.4.3.2 will be summarized by MedDRA SOC and PT for each treatment group.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at the End of Treatment and the Follow-Up visits. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (eg, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

Maximum postbaseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects in greater than 450 msec, greater than 480 msec, and greater than 500 msec during the treatment, and

- Number (percentage) of subjects with an increment of greater than 30 msec and greater than 60 msec from the baseline visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Other safety assessments including children and adolescent growth evaluations using CDC growth chart and bone age using x-ray of the hand, sexual maturation as measured in Tanner Staging, neuromuscular sign assessment for serotonin syndrome, signs and symptoms of priapism and prolactinemia, study drug effect on cognitive function assessed by WRAML-2, assessment of suicidality using C-SSRS, and mood assessment using CDI-2 will be also be summarized by treatment group at each scheduled visit.

9.7.2 Determination of Sample Size

The proposed sample size is based on the comparison of the primary efficacy endpoint, change from Baseline in BMI at Week 52 between the Belviq XR 20-mg treatment group and placebo group. Assuming a SD of 2.2 kg/m^2 and a 40% dropout rate, a sample size of 360 subjects in a 1:1 ratio (n=180 in the Belviq XR 20-mg treatment group; n=180 in the placebo group) will have at least 90% power to detect a treatment difference of 1 kg/m^2 in BMI, using a 2-sided t-test with α=0.05. Assuming the proportion of subjects achieving at least a 5% BMI reduction at Week 52 is 20% for the placebo group and a 40% dropout rate, this sample of 360 subjects (180 subjects for Belviq XR 20 mg and 180 subjects for placebo) will also have greater than 85% power to detect an absolute difference of 20% between the Belviq XR 20-mg group and placebo group, using a 2-sided Fisher's Exact test with α=0.05. The assumption used in the sample size calculation is based on the 2 pivotal lorcaserin studies, APD356-009 and APD356-011 in obese and overweight non-diabetic adult subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (gamma-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent or guardian) in Study 403 will participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their child or adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all Belviq XR study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

Appendix 3 Pharmacodynamic and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), and other biomarker analysis. These samples may be used for discovery or validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The pharmacogenetics (PG) samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events (AEs) related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PG, or other biomarker results are obtained that may have clinical relevance, Institutional Review Board review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

SIGNATURES

Authors:

PPD

Date

Neuroscience Business Group

Eisai Inc.

PPD

Date

Eisai Inc.

PPD

Date

Neuroscience Business Group

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Belviq XR® in Conjunction with Lifestyle Modification for Weight Loss in Obese Children and Adolescents, Age 9 to 17 Years
Investigational Product Name:	APD356/Belviq XR® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practices guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BELVIQ® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	APD356/BELVIQ® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	4
Approval Date:	FINAL 16 Apr 2015 (original protocol)
IND Number:	069888
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: APD356

Name of Active Ingredient: BELVIQ® (lorcaserin hydrochloride)

Study Protocol Title

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BELVIQ® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years

Investigators

Unknown

Site

Approximately 30 sites in the United States (US)

Study Period and Phase of Development

Approximately 24 months from first subject enrolled to last subject's last visit/last assessment

Phase 4

Objectives

- **Primary Objective**

  To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a 5% or greater reduction in body mass index (BMI) during 52 weeks of treatment with BELVIQ 20 mg administered once daily (QD) compared to placebo in obese adolescents.

- **Secondary Objectives**

  1. To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with ≥5% reduction in BMI (kg/m^2) after an initial 12 weeks of treatment with BELVIQ 20 mg administered QD compared to placebo in obese adolescents
  2. To demonstrate weight loss effect by mean change in BMI during 52 weeks of treatment of BELVIQ 20 mg administered QD compared to placebo in obese adolescents
  3. To demonstrate the effects of treatment with BELVIQ 20 mg QD by assessing:
     - Other weight loss effects (eg, proportion [%] of subjects achieving ≥10% BMI reduction, and change in waist circumference) at the end of 52 weeks of treatment
     - Effects on glycemia, insulin levels, and HOMA-IR during 52 weeks of treatment
     - Changes in cardiovascular risk factors associated with obesity (ie, hypertension, dyslipidemia, Metabolic Syndrome) during 52 weeks of treatment
  4. To assess the safety of BELVIQ, including the effects on growth by growth chart, sexual maturation measured by Tanner Staging scores, and signal of suicidal ideation/behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS)
  5. To assess the pharmacokinetics (PK) of lorcaserin in obese adolescents using population PK modeling
  6. To explore potential relationships between exposure to lorcaserin and pharmacodynamic

(PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving ≥5% and ≥10% reduction in BMI from baseline at Week 52, using population PK/pharmacodynamics (PD) modeling

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, age 12 to 17 years old. Approximately 360 subjects will be randomized in a 1:1 ratio to BELVIQ 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will receive BELVIQ 20 mg or placebo QD for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a diet and exercise program.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52, and a Follow-up Period extending from the end-of-treatment (EOT) visit to the end-of-study (EOS) visit.

All subjects will continue in the study until the 52-week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

Number of Subjects

Approximately 700 subjects will be screened to provide 360 randomized subjects.

Inclusion Criteria

1. Healthy, male or female, adolescents, age 12 to 17 years, at Screening with a BMI that is greater or equal to the US-weighted mean of the 95th percentile based on age and sex, but is less than 44 kg/m^2
2. Subjects in their junior year of high school or earlier, and their families are not planning to move away from the area for the duration of the study/assessments.
3. Subjects able and willing to comply with all aspects of the study including with a reduced-calorie diet and an increased physical activity program
4. Subjects considered to be in stable health in the opinion of the investigator.
5. Caregivers/guardians meeting following requirement:
    a. No history of Attention Deficit Hyperactivity Disorder (ADHD), substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia
    b. Able and willing to support, or/and supervise study participation in the opinion of the investigator including any existing physical, medical, or mental condition that prevents compliance with the protocol
    c. Able and willing to comply with all aspects of the study requirements for the caregivers/guardians

Exclusion Criteria

1. Clinically significant new illness within 1 month before randomization that may affect the subject's ability to fulfill the study requirements and significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension (PH) by objective assessments (ie, imaging modality or

cardiac catheterization)

4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease, as evidenced by a serum creatinine >1.5 × upper limit of normal (ULN), serum transaminases >3 × ULN, or total bilirubin >1.5 × ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia, ADHD, any DSM-5 depressive disorder, or suicidal ideation/behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (for example, Prader-Willi syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)
8. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
9. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer), or MAOIs within 30 days, prior to Randomization, including:

   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort and tryptophan
   - monoamine oxidase inhibitors (MAOIs)
   - linezolid
   - dextromethorphan (in any form, eg, OTC cold medicines)
   - lithium
   - tramadol
   - antipsychotics or other dopamine antagonists

   b) Others

   - antiseizure medications including valproic acid, zonisamide, lamotrigine
   - oral steroids (inhaled steroids are acceptable)
   - stimulant medications
   - benzodiazepines

10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before screening, including, but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or glucose intolerance), obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of BELVIQ within 6 months before screening or hypersensitivity to BELVIQ or any of

the excipients

13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of >5 kg within 3 months
14. Adherence to a very-low calorie (<1000/day) weight loss diet within 6 months
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before screening
17. Known to be human immunodeficiency virus (HIV) positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology
19. Malignancy within 5 years before screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a guardian to supervise study participation
21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <80], moderate to severe cognitive developmental delay, pervasive development disorders[(PDDs], autism)
22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening, or any time between screening and randomization
23. Uncontrolled hypertension, defined as blood pressure (BP) in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days; subjects who had uncontrolled hypertension at screening can be rescreened >1 month following initiation or adjustment of antihypertensive therapy.
24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator including any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Females of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 30 days after study drug discontinuation.
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period or for 30 days after study drug discontinuation.
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the

same contraceptive during the study or for 30 days after study drug discontinuation.

(NOTE: All females will be considered to be of childbearing potential unless they are have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

29. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 30 days after study drug discontinuation). No sperm donation is allowed during the study period or for 30 days after study drug discontinuation.

Study Treatment(s)

Test drug

BELVIQ (lorcaserin hydrochloride) will be provided as blue-colored, round, film-coated biconvex tablets with one 20-mg tablet administered orally, QD.

Comparator Drug

Matching placebo, 1 tablet administered orally, QD

Duration of Treatment

Prerandomization Phase: 30 days

Randomization Phase: 56 weeks

Concomitant Drug/Therapy

Other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. Any of the following serotonergic agents in combination with BELVIQ are prohibited. Over-the-counter cold medicines containing dextromethorphan can be used for up to 7 days with study medication temporarily stopped for that time period and resumed the next day after the OTC cold medicine is stopped.

Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort and tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

Others

- antiseizure medications including valproic acid, zonisamide, lamotrigine
- oral steroids (inhaled steroids are acceptable)
- stimulant medications
- benzodiazepines

Assessments

Efficacy Assessments

- Body weight and height will be assessed to measure BMI and to calculate the proportion (%) of patients achieving ≥5% and ≥10% BMI reduction at Week 52.
- Measurement of systolic BP, diastolic BP, heart rate (HR), triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting plasma glucose, fasting insulin, and haemoglobin A1c (HbA1c) to assess cardiovascular and metabolic profiles
- Metabolic Syndrome as defined by the International Diabetes Federation (IDF)
- Pre-hypertension and primary hypertension as defined by Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents
- Dyslipidemia as defined by Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

Pharmacokinetic Assessments

Plasma lorcaserin concentrations will be measured at Weeks 12, 28, 36, and 52 for analysis of population PK. At Weeks 12, 24, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: predose (within 30 minutes prior to dosing) and within 1 to 3 hours postdose. At the Week 36 visit, subjects will take the morning dose at home, and 1 sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours postdose.

Pharmacodynamic Assessments

- Proportion (%) of patients achieving ≥5% and ≥10% BMI reduction
- BMI change from baseline

Other pharmacodynamic endpoints will be considered based on the data at the end of the study to explore their relationships with exposure to lorcaserin

Pharmacogenomic/Pharmacogenetic Assessments

At the time of randomization, when applicable, a blood sample will be taken for potential investigation of genetic variability associated with genotypes relating to response to BELVIQ, weight loss, susceptibility to diabetes, and their associated risk factors.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), laboratory evaluation for hematology, blood chemistry, and urine values; neuropsychiatric events, periodic measurement of vital signs, and performance of physical examinations. Study drug effect on adolescent growth will be evaluated using the US Center for

Disease Control (CDC) growth chart and a full physical examination. Adolescent sexual maturation will be evaluated by self-reported changes in Tanner Staging.

The C-SSRS will be used to assess all adolescent subjects in the study for any signal of depression and suicidal ideation/behavior.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS).

Statistical Methods

Study Endpoints

Primary Endpoint

- Proportion (%) of patients achieving ≥5% BMI reduction at Week 52

Secondary Endpoints

- Proportion (%) of patients achieving ≥10% BMI reduction at Week 52
- Proportion (%) of patients achieving ≥5% BMI reduction at Week 12
- Change and percent change in BMI from Baseline to Week 52
- Change in waist circumference from Baseline to Week 52
- Change in HbA_{1c} from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR (HOMA-IR=glucose [mg/dL] x insulin [mU/L] /405) from Baseline to Week 52
- Change in blood pressure (systolic and diastolic) from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion of subjects with Metabolic Syndrome at Week 52
- Proportion (%) of subjects with pre-hypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects who received at least 1 dose of study drug and had at least 1 postdose measurement.
- The Intent-to-Treat set (ITT) is the group of all randomized subjects regardless of whether they took study drug or not.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, violations of inclusion/exclusion criteria, and have BMI data at Baseline, Week 12, and Week 52. The determination of subjects to be excluded from this population based on the

above criteria and list of major protocol violations will be included in the SAP and finalized prior to data base lock.

- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid lorcaserin plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of body weight.

Efficacy Analyses

For the primary and secondary endpoints, a 2-sided α=0.05 significance level will be used.

Primary Analysis

- The proportion of subjects achieving ≥5% BMI reduction will be analyzed using logistic regression model with treatment and site as factors and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 52, as nonresponders (did not achieve ≥5% BMI reduction).

Secondary Analyses

- The proportion of subjects achieving ≥5% BMI reduction will be analyzed using logistic regression model with treatment and site as a factors, and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 12. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 12, as nonresponders (did not achieve ≥5% BMI reduction).
- Change and percent change from baseline in BMI will be analyzed using an analysis of covariance model with treatment and site as factors and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52 using the last observation carried forward (LOCF) approach. The FAS analysis set will be used for this analysis. Additional sensitivity analyses will be performed using model-based imputation methods that will be described separately in the SAP.
- Rates of growth in height will be summarized by the height distribution of percent change from Baseline to Week 52 by treatment group. The Safety Analysis Set will be used for this analysis.
- Tanner Staging (II, III, IV, and V) will be summarized using shift tables from Baseline to Week 52 by treatment group. The Safety Analysis Set will be used for this analysis.
- C-SSRS: The incidence of suicidal ideation or suicidal behavior will be summarized by treatment groups. The Safety Analysis Set will be used for this analysis.
- The change from baseline for the endpoints HbA1c, fasting plasma glucose, fasting insulin, HOMA-IR, waist circumference, blood pressure (systolic and diastolic), and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) will be analyzed using a mixed-effects model with repeated measures with treatment and site as factors and baseline as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis.

- The proportion of subjects achieving ≥10% BMI reduction will be analyzed using logistic regression model with treatment and site as factors, and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 52 as nonresponders (did not achieve ≥10% BMI reduction).
- A logistic regression model with treatment and site as factors will be used to analyze the following endpoints. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for these analyses. Sensitivity analysis will be conducted using LOCF for subjects with missing data at Week 52.
    - Proportion (%) of subjects with confirmed pre-hypertension or primary hypertension
    - Proportion (%) of subjects with dyslipidemia
    - Proportion (%) with metabolic syndrome that met at least 2 IDF criteria

Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics/demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration (C_{max}) and the area under the concentration-time curve from time zero to 24 hours at steady-state ($AUC_{0\text{-}24,ss}$) will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

Pharmacodynamic Analyses

Proportion (%) of patients achieving ≥5% and ≥10% BMI reduction, and BMI change from baseline will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (ie, BMI change, percentage of BMI change, proportion [%] of patients achieving ≥10% BMI reduction, and waist circumference from baseline) will also assessed as PD analysis. The PK/PD analysis set will be used for this analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD modeling will be used to explore the relationship between exposure to BELVIQ and response, including but not limited to change in BMI from baseline and the probability of achieving ≥5% and ≥10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

Pharmacogenomic/Pharmacogenetic Analyses

A blood sample for potential investigation of genetic variability associated with genotypes relating to response to BELVIQ, weight loss, susceptibility to diabetes, and their associated risk factors will be taken at the time of randomization in the study, where applicable.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical examination), suicidal ideation/behavior (C-SSRS), neuropsychiatric events, out-of-normal-range laboratory safety test variables, along with change from

baseline in laboratory safety test variables, and vital sign measurements at the end of treatment will be summarized by treatment group using descriptive statistics.

Interim Analyses

Not applicable

Sample Size Rationale

A sample size of 360 subjects in a 1:1 ratio (n=180 in the BELVIQ 20-mg QD treatment group: n=180 in the placebo group) will have 90% power to detect a 20% difference between treatment groups in the proportions of subjects with at least 5% reduction in BMI, assuming the placebo response is 20%, using a 2-sided test and α=0.05, assuming a 35% dropout rate. The assumption is based on lorcaserin adult Phase 3 and adolescent studies with orlistat and sibutramine.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC_{inf}	area under the concentration × time curve from time zero to infinity
$AUC_{0-24,ss}$	area under the concentration - time curve from zero time to 24 hours at steady state
ß-hCG	beta-human chorionic gonadotropin
BMI	body mass index defined as weight divided by height squared
BP	blood pressure
CA	Competent Authority
CDC	Center for Disease Control
C_{max}	maximum observed concentration
CRA	clinical research associate
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	curriculum vitae
DEA	Drug Enforcement Administration
ECG	Electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH E6	International Conference on Harmonisation Good Clinical Practice
IDF	International Diabetes Federation
IEC	Independent Ethics Committee

Abbreviation	Term
IRB	Institutional Review Board
ITT	Intent –to-Treat
LDL	low density lipoprotein
LNH	low/normal/high
LOCF	Last Observation Carried Forward
IxRS	interactive voice and/or web response system
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PD	Pharmacodynamics
PDD	pervasive development disorders
PH	pulmonary hypertension
PI	principal investigator
PK	Pharmacokinetics
PT	preferred term
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SI	Système International
SNRIs	serotonin norepinephrine reuptake inhibitors
SOC	System Organ Class
SOPs	standard operating procedures
SSRI	selective serotonin reuptake inhibitors
T2DM	type 2 diabetes mellitus
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
US	United States
US 21 CFR	United States Code of Federal Regulations
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation Good Clinical Practice (ICH E6), Section 3, and any local regulations (eg, Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA]), change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. The adolescent participant will provide written assent and the caregiver/guardian will provide written informed consent.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (Federal Regulations, Title 21 CFR Part 50, for studies in the United States [US]). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Obesity

Obesity has become a global epidemic as well as a serious public health concern. In the United States (US), the prevalence of obesity in adolescents between 12 and 19 years of age has almost doubled over the past 2 decades. The rate increased from 10.5% between 1988 and 1994 to 20.5% between 2011 and 2012 (CDC/NCHS, 2013). Obesity in adolescents, defined in the US as ≥95th percentile in gender- and age-specific body mass index (BMI), continues to grow at an alarming rate in the US and globally. Based on data (Wang and Lobstein, 2006) using various criteria for the definition of obesity that included more than 30 countries in Europe, North America, Asia, and West Pacific countries, prevalence rates in these countries also have increased significantly, comparable to that in the US.

Adolescent obesity has many negative implications for both the health and well-being of the individual as well as for society. These include increased susceptibility to a host of diseases, chronic health disorders, psychological disorders, and premature death (Flegal, et al., 2005; Rofey, et al., 2009). Increases in the prevalence of overweight and obese adolescents may result in a decrease in life expectancy for the first time in 200 years.

As a result, there is a significant impact to the cost of healthcare. It is estimated that medical costs due to overweight adolescents are approximately more than $14 billion per year in the US (Trasande, et al., 2009). Obesity-related medical costs in general are expected to rise significantly, especially because today's obese children are likely to become tomorrow's obese adults.

Current approaches to weight management include lifestyle modification, pharmacotherapy, and invasive bariatric procedures. Lifestyle modification involves a combination of diet, exercise, and behavioral change, and is the preferred and essential strategy for weight management in obese and overweight individuals. Although lifestyle modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs and is often combined with lifestyle modification to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise.

The current standard of care for treatment of obesity in pediatric subjects ranges from lifestyle intervention in children younger than 8 years old to use of pharmacotherapy in adolescents older than 12 years (McGovern, 2008; Spear, 2007). Xenical® (orlistat) is currently the only product available for weight control in obese adolescent patients 12 to 16 years of age; however, it is associated with gastrointestinal side effects (Xenical PI. 2006), and the treatment effect of Xenical is modest. In a study that included 539 obese adolescents with BMI >97th percentile, Xenical demonstrated a 0.86 BMI reduction relative to placebo after 52 weeks of treatment (-0.55 BMI in the Xenical treatment group versus +0.31 BMI in the placebo group) (FDA, 2003; Chanoine JP, 2005).

7.1.1 APD356/BELVIQ (lorcaserin hydrochloride)

7.1.1.1 Mechanism of Action

BELVIQ® is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 June 2012 as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with a BMI ≥30 kg/m^2 (obese), or adult patients with a BMI ≥27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

7.1.1.2 Clinical Experience with APD356/BELVIQ (lorcaserin hydrochloride)

The Phase 3 clinical evaluation of BELVIQ in clinical studies of more than 7700 adult subjects, including 604 subjects with type 2 diabetes mellitus (T2DM), demonstrated clinically meaningful efficacy, and a safety profile that includes minimal and easily managed risks. Additionally, in studies APD356-009 and APD356-011, more than 2% of the subjects developed biochemical criteria for T2DM during the study (hemoglobin A_{1c} [HbA_{1c}] ≥6.5). The proportion of subjects developing new criteria for diabetes was 1.6-fold greater in the placebo as compared with the BELVIQ 20 mg once daily (QD) group (P=0.003). In the pooled efficacy analyses, the BELVIQ 20 mg QD dose met the following prespecified endpoints:

- A significantly greater proportion of subjects taking BELVIQ (47%) lost ≥5% of baseline body weight at 1 year as compared to placebo (23%). A significantly greater proportion of subjects taking BELVIQ (22.4%) lost ≥10% of baseline body weight at 1 year as compared to placebo (8.7%).

- The mean weight loss at 1 year in subjects taking BELVIQ (-5.8 kg) was significantly greater than that in subjects taking placebo (-2.5 kg).

- Glycemic benefits were also demonstrated by a 0.5% HbA_{1c} reduction among subjects with T2DM and reduction in incidence of new diabetes in the prediabetes population compared to placebo

In adolescent obese populations, it is anticipated that BELVIQ will result in similar effects. As part of the FDA post marketing requirements, this study is designed to characterize the efficacy and safety of BELVIQ in adolescent obese populations in the US; it is also intended to support an indication for chronic weight management for obese adolescents.

7.2 Study Rationale

There is no specific FDA guidance for the approval of a weight loss product in adolescents. In adults, the Division's 2007 draft Guidance for Industry Developing Products for Weight Management indicate that the product needs to satisfy either of the following mean or categorical criteria after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant, or
- The proportion of subjects who lose ≥5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion of subjects in the placebo-treated group who lose ≥5% of baseline body weight, and the difference between groups is statistically significant.

The FDA awarded a weight management indication for BELVIQ based on Phase-3 study results which achieved the categorical criteria. In a Phase 3 study, a significantly greater proportion of subjects taking BELVIQ (47%) lost ≥5% of baseline body weight at 1 year as compared to placebo (23%). It is anticipated that a similar effect will be demonstrated in an obese adolescent population, where weight loss will be assessed using BMI (kg/m^2) measurements to account for growth. In this study, the objective is to demonstrate that BELVIQ will achieve a greater proportion (%) of subjects with ≥5% reduction in BMI during 52 weeks of treatment with BELVIQ 20 mg administered QD compared to placebo in obese adolescents.

There are limited clinical studies of weight loss products in obese adolescent populations. In the Phase 3 orlistat study mentioned above, the proportion of subjects who lost at least 5% body weight is relatively low. At the end of the study at Week 52, only 26.5% of subjects achieved a 5% or more BMI reduction compared to 15.7% in the placebo group. In a sibutramine Phase-3 study in obese adolescents, a substantially higher proportion of subjects (69%) treated with sibutramine achieved at least 5% BMI reduction compared to 21% of subjects in the placebo group (Berkowitz. 2006). Unlike the weight loss effect of BELVIQ in adults and sibutramine in adolescents, subjects in the orlistat study started to increase their BMI after 6 months of treatment (Chanoine, 2005).

In this proposed study, it is assumed that 20% of subjects in the placebo group will achieve at least a 5% reduction in BMI, based mostly on placebo group results in the above-mentioned sibutramine study (21%) and the BELVIQ Phase-3 studies (23%).

After 1 year, pooled analyses from the two Phase 3 BELVIQ pivotal studies showed that 47% of the BELVIQ-treated subjects achieved at least a 5% reduction in weight compared with 23% of the placebo subjects. This between-group difference of 24.5% is the basis for the conservative assumption of a 20% effect size in the current study.

In addition, the total sample size of 360 subjects will be adequate to assess safety and exposure, based on previous adolescent studies with weight management products (orlistat and sibutramine) (FDA, 2003; Chanoine, 2005; Berkowitz, 2006), and other metabolic/dyslipidemia medication products (ezetimibe/simvastatin) (FDA, 2007).

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with a 5% or greater reduction in BMI during 52 weeks of treatment with BELVIQ 20 mg administered once daily (QD) compared to placebo in obese adolescents.

8.2 Secondary Objectives

The secondary objectives of the study are:

1. To demonstrate weight loss efficacy by achieving a greater proportion (%) of subjects with ≥5% reduction in BMI (kg/m^2) after an initial 12 weeks of treatment with BELVIQ 20 mg administered QD compared to placebo in obese adolescents
2. To demonstrate weight loss effect by mean change in BMI during 52 weeks of treatment with BELVIQ 20 mg administered QD compared to placebo in obese adolescents.
3. To demonstrate the effects of treatment with BELVIQ 20 mg QD by assessing:
   - Other weight loss effects (eg, proportion [%] of subjects achieving ≥10% BMI reduction, and change in waist circumference) at the end of 52 weeks of treatment
   - Effects on glycemia, insulin levels, and HOMA-IR during 52 weeks of treatment
   - Changes in cardiovascular risk factors associated with obesity (ie, hypertension, dyslipidemia, Metabolic Syndrome) during 52 weeks of treatment
4. To assess the safety of BELVIQ, including the effects on growth by growth chart, sexual maturation measured by Tanner Staging scores, and signal of suicidal ideation/behavior with the Columbia-Suicide Severity Rating Scale (C-SSRS)
5. To assess the pharmacokinetics (PK) of lorcaserin in obese adolescents using population PK modeling
6. To explore potential relationships between exposure to lorcaserin and pharmacodynamic (PD) parameters including but not limited to reduction from baseline in BMI and probability of achieving ≥5% and ≥10% reduction in BMI from baseline at Week 52, using population PK/pharmacodynamics (PD) modeling

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in obese adolescents, age 12 to 17 years old. Approximately 360 subjects will be randomized in a 1:1 ratio to BELVIQ 20 mg QD (180 subjects) and placebo (180 subjects). Subjects will receive BELVIQ 20 mg or placebo QD for up to 52 weeks. Throughout the duration of the study, subjects will be encouraged to adhere to a lifestyle modification program that includes diet and exercise counseling (see Appendix 2).

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consists of 1 visit during which subjects will be screened for eligibility. The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last for a maximum of 52 weeks, with visits at Weeks 1, 5, 8, 12, 20, 28, 36, 44, and 52; the Follow-up Period will extend from the end-of-treatment (EOT) visit to the end-of-study (EOS) visit.

All subjects will continue in the study until the 52 week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion.

9.1.1 Prerandomization/Pretreatment Phase

Screening will occur during the Prerandomization Phase at Visit 1.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain the informed consent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Randomization/Treatment Phase

The Randomization Phase will consist of 2 periods, the Treatment Period and the Follow-up Period. The Treatment Period assessments and timing thereof are shown in Section 9.5.2.

9.1.3 Extension Phase

Not applicable

9.2 Discussion of Study Design, Including Choice of Control Groups

The proposed dose and dosing frequency in this study is 20 mg QD which is the FDA-approved regimen for obesity in adults. The PK parameters of a single 10-mg dose of BELVIQ were evaluated in healthy, adolescent obese subjects in Study APD356-025. Overall, the PK parameters of BELVIQ and its main metabolites, M1 and M5, were similar to those in adults. Following a single, oral administration of BELVIQ 10 mg to a total of

8 healthy adolescent (age 12 to 17 years, inclusive) obese subjects, the mean maximum concentration observed (C_{max}) and the area under the concentration- time curve from time zero to infinity ($AUC_{(0\text{-}inf)}$) were 36.5 ng/mL and 464 hr·ng/mL, respectively. The mean BELVIQ terminal phase half-life ($t_{1/2}$) was 9.70 hours, similar to that observed in adults, thus supporting a similar dosing frequency (ie, once daily) in adolescent subjects.

The targeted study population comprises 360 obese adolescents 12 to 17 years of age, inclusive.

Obese adolescents will be identified using gender- and age-specific BMI measurement. Obesity in adolescents is defined by US Expert committee recommendations as BMI ≥95th percentile (Barlow, 2007).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints

9.3 Selection of Study Population

Approximately 700 subjects will be screened to ensure that 360 subjects will be randomized.

Subjects who do not meet all inclusion criteria or do meet any exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Healthy, male or female adolescents, age 12 to 17 years, at Screening with a BMI that is greater or equal to the US weighted mean of the 95th percentile based on age and sex, but is less than 44 kg/m^2.

2. Subjects in their junior year of high school or earlier, and their families are not planning to move away from the area for the duration of the study/assessments

3. Subjects able and willing to comply with all aspects of the study including with a reduced-calorie diet and an increased physical activity program

4. Subjects considered to be in stable health in the opinion of the investigator

5. Caregivers/guardians meeting following requirement:

    a. No history of Attention Deficit Hyperactivity Disorder (ADHD, substance abuse, depression, suicidal ideation/behavior, bipolar disorder, or schizophrenia)

b. Able and willing to support, or/and supervise study participation in the opinion of the investigator including any existing physical, medical, or mental condition that prevents compliance with the protocol
c. Able and willing to comply with all aspects of the study requirements for the caregivers/guardians

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant new illness within 30 days before randomization that may affect the subject's ability to fulfill the study requirements and significantly confound the assessments
2. Subjects who cannot swallow investigational products
3. Documented pulmonary hypertension (PH) by objective assessments (ie, imaging modality or cardiac catherization)
4. Known valvular disease defined by clinical diagnosis or most recent echocardiography. History of valvular disease is allowed if it has been corrected by valve replacement or repair.
5. Significant renal or hepatic disease, as evidenced by a serum creatinine >1.5 × upper limit of normal (ULN), serum transaminases >3 × ULN, or total bilirubin >1.5 × ULN in absence of Gilbert's syndrome
6. Any history of anorexia or bulimia, ADHD, any DSM-5 depressive disorder, or suicidal ideation/behavior, bipolar disorder, or schizophrenia
7. Known secondary causes (chromosomal, endocrine, or metabolic) for obesity (for example, Prader-Willi syndrome, Down's Syndrome, untreated hypothyroidism, Cushing's syndrome, daily systemic corticosteroid exposure for longer than 30 days, history of significant exposure to corticosteroids for chronic illness during the past year, and known genetic causes of obesity)
8. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month before Screening
9. Use of any of the following medications:

   a) Serotonergic drugs within 7 days (or 5 half-lives, whichever is longer), or MAOIs within 30 days, prior to Randomization, including:

   - selective serotonin reuptake inhibitors (SSRIs)
   - serotonin norepinephrine reuptake inhibitors (SNRIs)
   - tricyclic antidepressants (TCAs)
   - bupropion
   - triptans
   - St. John's Wort and tryptophan
   - monoamine oxidase inhibitors (MAOIs)

- linezolid
- dextromethorphan (in any form, eg, OTC cold medicines)
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b) Others

- antiseizure medications including valproic acid, zonisamide, lamotrigine
- oral steroids (inhaled steroids are acceptable)
- stimulant medications
- benzodiazepines

10. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months before Screening, including, but not limited to pergolide, ergotamine, methysergide, and cabergoline
11. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) other than prediabetes (impaired fasting glucose or glucose intolerance), obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease
12. Use of BELVIQ within 6 months before Screening or hypersensitivity to BELVIQ or any of the excipients
13. Significant change in diet or level of physical activity within 1 month before dosing or change in weight of >5 kg within 3 months
14. Adherence to a of very-low calorie (<1000/day) weight loss diet within 6 months
15. History of alcohol or drug dependence or abuse
16. Recreational drug use within 2 years before Screening
17. Known to be human immunodeficiency virus (HIV) positive
18. Active viral hepatitis (B or C) as demonstrated by positive serology
19. Malignancy within 5 years before Screening
20. Unable to attend scheduled visits (eg, lack of transportation) or lack of a guardian to supervise study participation
21. Special needs subjects who are unable to comprehend study-related instructions (eg, mild to profound mental retardation [IQ <80], moderate to severe cognitive developmental delay, pervasive development disorders (PDD), autism
22. Ongoing epilepsy or other seizure disorder, or use of medications for a seizure disorder within 6 months of screening, or any time between screening and randomization
23. Uncontrolled hypertension, defined as blood pressure (BP) in the 95th percentile or greater for age, sex, and height on 2 separate readings recorded on 2 separate days;

subjects who had uncontrolled hypertension at Screening can be rescreened >1 month following initiation or adjustment of antihypertensive therapy.

24. Currently enrolled in another clinical study or has used any investigational drug or device within 30 days before providing informed consent
25. Planned bariatric surgery during the study
26. Not suitable to participate in the study in the opinion of the investigator including any existing physical, medical, or mental condition that prevents compliance with the protocol
27. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Females of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 30 days after study drug discontinuation.
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period or for 30 days after study drug discontinuation.
    c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 30 days after study drug discontinuation.

(NOTE: All females will be considered to be of childbearing potential unless they are have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

29. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 30 days after study drug discontinuation). No sperm donation is allowed during the study period or for 30 days after study drug discontinuation.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered a single tablet of BELVIQ 20 mg or placebo orally QD.

BELVIQ (lorcaserin hydrochloride) is a (US) Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C – IV).

BELVIQ XR will be provided as blue-colored, round, film-coated, biconvex 20-mg tablets (microcrystalline cellulose; mannitol, hypromellose 2208, ethylcellulose dispersion Type B, hypromellose 2910; colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide yellow, iron oxide red, and magnesium stearate). BELVIQ XR and matching placebo will be supplied by the sponsor in labeled containers.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of BELVIQ

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \bullet 0.5\ H_2O$
- Molecular weight: 241.16 g/mol (hemihydrate form)

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Study drug will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The clinical study labels will contain, but are not limited to the following requirements:

1. Name and address of the sponsor
2. Pharmaceutical dosage form, quantity of dosage units, and strength
3. Lot number or Packaging Reference number
4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. US Caution Statement: "CAUTION: New Drug – Limited by Federal (US) law to investigational use."

All packaging and labeling will be performed according to Good Manufacturing Practices and GCP guidelines.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Schedule IV Controlled Drugs (US sites). Study drug must be kept in a secure location as required by DEA regulations and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain any discrepancies.

A Drug Dispensing Log must be kept current and should contain at least the following information:

- Identification (subject ID number and initials) of the subject to whom the study drug was dispensed
- The dates and unique kit/carton identifiers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Prerandomization Phase, subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1. Each treatment group will receive either BELIVIQ or placebo QD. Randomization will be performed centrally by an interactive voice and/or web response

system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization, the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection and Timing of Dose for Each Subject

Subjects should take the study medication once daily, and be encouraged to take the study medication with an adequate amount of water (8 oz. or 240 mL).

9.4.5 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

9.4.6 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF'

Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. Any of the following serotonergic agents in combination with BELVIQ is prohibited, with the exception that OTC cold medicines containing dextromethorphan can be used for up to 7 days and study medication is temporarily stopped for that time period (and should be resumed the next day after the OTC cold medicine is stopped).

a. Serotonergic drugs

- SSRIs
- SNRIs
- TCAs
- bupropion
- triptans
- St. John's Wort and tryptophan
- MAOIs
- linezolid
- dextromethorphan
- lithium
- tramadol
- antipsychotics or other dopamine antagonists

b. Others

- antiseizure medications including valproic acid, zonisamide, lamotrigine
- oral steroids (inhaled steroids are acceptable)
- stimulant medications
- benzodiazepines

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRAs will review treatment compliance during site visits and at the completion of the study.

Subjects will return unused study drug approximately every 4 weeks and be given a new 4-week supply per visit schedule; pill counts will be made by study staff on returned medication.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted

- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal PI and all sub-investigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the current Controlled Substance Registration Certificate- Form DEA 223 (US sites only). Must be appropriate to handle schedule IV products and not be expired.

The investigational product can only be shipped to the exact address detailed on the site's form DEA 223. If a site requires drug to be shipped to a particular location, then an appropriate form DEA 223 certificate must be provided for that location.

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health

authority (eg, FDA, Medicine and Healthcare Products Regulatory Agency). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the first visit. Demography information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the first visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.3 Efficacy Assessments

- Body weight and height will be assessed to measure change in BMI from Baseline to Week 52 and to calculate the proportion (%) of patients achieving ≥5% and ≥10% BMI reduction at Week 52.

- Measurement of systolic BP, diastolic BP, heart rate (HR), triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein

(LDL) cholesterol, fasting plasma glucose, fasting insulin, and HbA_{1c} will be used to assess the change in cardiovascular and metabolic profiles from Baseline to Week 52.

- Metabolic Syndrome as defined by the International Diabetes Federation (IDF) (IDF, 2014)

- Pre-hypertension and primary hypertension as defined by Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report Pediatrics. 2011; 128:S213-S256).

- Dyslipidemia as defined by Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report Pediatrics. 2011; 128:S213-S256).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (approximately 4 mL each) for PK assessments will be collected at Weeks 12, 28, 36, and 52 for population/PK analyses. At Weeks 12, 28, and 52, subjects will be instructed to take their morning dose at the clinic. Two blood samples for determination of plasma concentrations of lorcaserin will be taken at each of these visits: predose (within 30 minutes prior to dosing) and within 1 to 3 hours postdose. At the Week 36 visit, subjects will take the morning dose at home, and 1 sample for determination of plasma concentrations of lorcaserin will be collected at the investigational site within 4 to 6 hours postdose.

Plasma lorcaserin concentrations will be measured using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS) method. The collection, handling, and shipping procedures for PK samples will be described in a manual to be provided to the study sites.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

- Proportion (%) of patients achieving ≥5% and ≥10% BMI reduction
- BMI change from baseline

Other PD endpoints will be considered based on the data at the end of the study to explore their relationships with exposure to lorcaserin.

9.5.1.4.3 PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs), ECGs, laboratory evaluations for hematology, blood chemistry, and urine values; neuropsychiatric events, periodic measurements of vital signs, and performance of physical examinations. Adolescent growth will be evaluated using the US Center for Disease Control (CDC) growth chart at Baseline, and Weeks 5, 12, 28, 36, 52, and at Follow-up, and a full physical examination at Baseline and Weeks 12, 28, 36, 52, and at Follow-up. Adolescent sexual maturation will be evaluated by self-reported changes in Tanner Staging at Baseline, Week 28, and Week 52.

The C-SSRS will be used to assess all adolescent subjects in the study with any signal of depression and suicidal ideation/behavior.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is BELVIQ (lorcaserin hydrochloride).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, electrocardiogram (ECG) or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Screening Disposition CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious AEs will be collected for 30 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is >450 ms and there is an increase of >60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments

- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria:

- Serotonin syndrome (must have at least one of the following: Spontaneous clonus; Inducible clonus PLUS agitation or diaphoresis; Ocular clonus PLUS agitation or diaphoresis; Tremor PLUS hyperreflexia; Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus)
- Psychosis, suicidal behavior

- Priapism
- New onset valvular heart disease
- New onset PH
- Malignant neoplasms, with the exception of basal cell and squamous cell carcinomas of the skin
- Fibroadenomas of the breast or ductal carcinoma in situ

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, globulin, glucose, HbA_{1c}, HDL cholesterol, lactate dehydrogenase, LDL cholesterol, phosphorus, total protein, total cholesterol, triglycerides, prolactin, uric acid, urine ß-hCG
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ß-hCG = beta-human chorionic gonadotropin, HbA_{1c} = hemoglobin A_{1c} , HDL = high density lipoprotein, LDL = low density lipoprotein, RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 HEIGHT MEASUREMENTS

Height (cm) measurements will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF. Results of the C-SSRS will be reviewed.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 2).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

An assessment of suicidality using the C-SSRS will be performed at Baseline and at study visits as designated in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

A urine pregnancy test will be performed at designated time points as specified in the Schedule of Procedures/Assessments (Table 2).

9.5.1.6.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 2). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the Schedule of Procedures/Assessments for the study.

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
Informed Consent	X													
Demography	X													
Medical History	X	X												
Prior/concomitant medication assessments	X	X	X	X	X	X	X	X	X	X	X		X	X
Inclusion/exclusion criteria	X	X												
Physical Examination	X	X				X		X	X		X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X		X		X		X	X		X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist/Hip circumference	X	X		X		X		X	X		X	X	X	X
Routine clinical laboratory tests	X	X	X	X		X		X			X	X	X	X
Urinalysis	X		X	X		X		X	X		X	X	X	X
HbA_{1c} sampling	X					X		X			X			X
Drugs of abuse screen	X													
Pregnancy test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization		X												

Table 2 Schedule of Procedures/Assessments in Study APD356-A001-403

Phase:	**Prerandomization**[a]		**Randomization**										**Other**	
Period:	**Screening**		**Treatment**									**Follow-up**		
Visit Number:	1	2[a]	3	4	5	6	7	8	9	10	11 (EOT)	EOS	Un-scheduled	Early discon-tinuation
Day:	-30 to -1	1												
Weeks[b,c]:		0	1	5	8	12	20	28	36	44	52	56		
Procedure														
IxRS	X	X		X	X	X	X	X	X	X	X			
Study drug dispensing		X		X	X	X	X	X	X	X			X	
Collect study medication				X	X	X	X	X	X	X	X	X	X	X
Drug accounting and compliance			X	X	X	X	X	X	X	X	X		X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
US CDC growth chart	X	X		X		X		X			X	X	X	X
Tanner Staging	X	X						X			X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample						X		X	X		X			X
Pharmacogenomic sample	X													
Prolactin		X				X		X			X			X
ECG	X							X			X			X
Lifestyle modification counseling[d]		X	X	X	X	X	X	X	X	X			X	

CDC = Center for Disease Control, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EOS = end of study, EOT = end of treatment, HBA_{1c} = hemoglobin A_{1c}, IxRS = interactive voice and/or web response system, PK = pharmacokinetics, US = United States,

a: Baseline measurements will be collected on Day 1, prior to drug administration unless specified otherwise.

b: Window ±7 days for all visits after Visit 2 except for Weeks 12 and 28 (the window for these visits will be broader at ±14 days). Week is shown unless otherwise indicated.

c: On Weeks 12, 28, and 52, subjects will take the morning dose at the clinic, and 2 blood samples for determination of plasma concentrations of lorcaserin will be taken: predose (within 30 minutes prior to dosing) and within 1 to 3 hours postdose (time in which the dose was taken on the night previous to the visit must be recorded). On Week 36 the subjects will take the morning dose at home (time of morning dosing at home must be recorded), and 1 blood sample for determination of plasma concentrations of lorcaserin will be collected at the investigational within 4 to 6 hours postdose.

d: Lifestyle modification counseling will also be performed at Weeks 3, 24, 32, 40, and 48in addition to counseling at the visits in the schedule of assessments table above.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Assessments (Table 2) for details, giving particular attention to all footnotes.

9.5.2.3 Total Volume of Blood Sampling

Table 3 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 3 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Visits 2, 3, 4, 6, 8; 11/EOT, EOS	12×8=96
PK blood sampling	4	Visits 6, 8, 9, and 11/EOT (2 samples each)	8×4=32
Total			128

EOS = end of study, EOT = end of treatment, PK = pharmacokinetics.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of obesity.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the through the last visit and for 30 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (serotonin syndrome, psychosis, suicidal behavior, priapism, new onset valvular heart disease, new onset PH, malignant neoplasms [with the exception of basal cell and squamous cell carcinomas of the skin], and fibroadenomas of the breast or ductal carcinoma *in situ*) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects will continue in the study until the 52 week evaluation is completed. Subjects who discontinue treatment prematurely will be followed up until study completion. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 2).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the CRF. The DEA Registrant has the responsibility to comply with local, state and Federal laws to notify the Field Division Office of the Drug Enforcement Administration of any theft or significant loss of any controlled substances upon discovery of such theft or loss.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

- Proportion (%) of patients achieving ≥5% BMI reduction at Week 52

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- Proportion (%) of patients achieving ≥10% BMI reduction at Week 52
- Proportion (%) of patients achieving ≥5% BMI reduction at Week 12
- Change and percent in BMI from Baseline to Week 52
- Change in waist circumference from Baseline to Week 52
- Change in HbA1c from Baseline to Week 52
- Change in fasting glucose, fasting insulin, and HOMA-IR (HOMA-IR=glucose [mg/dL] x insulin [mU/L] /405) from Baseline to Week 52
- Change in blood pressure (systolic and diastolic) from Baseline to Week 52
- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from Baseline to Week 52
- Proportion of subjects with Metabolic Syndrome at Week 52
- Proportion (%) of subjects with pre-hypertension or primary hypertension at Week 52
- Proportion (%) of subjects with dyslipidemia at Week 52

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of all randomized subjects who received at least 1 dose of study drug and had at least 1 postdose measurement.
- The Intent-to-Treat set (ITT) is the group of all randomized subjects regardless of whether they took study drug or not.
- Per-Protocol Analysis Set (PP) is the group of all randomized subjects who are 80% or greater compliant with study medication, completed the study, have no major protocol deviations, violations of inclusion/exclusion criteria, and have BMI data at Baseline, Week 12, and Week 52. The determination of subjects to be excluded from this population based on the above criteria and list of major protocol violations will be included in the SAP and finalized prior to data base lock.
- The PD Analysis Set is the group of subjects who had sufficient PD data to derive at least 1 PD parameter.
- The PK Analysis Set is the group of all randomized subjects from whom at least 1 valid BELVIQ plasma concentration was obtained with associated documented dosing history.
- The population PK/PD set is the group of randomized subjects with PK information and who have at least 1 adequately documented measurement of body weight.

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

For study completion, the number (percentage) of treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on the CRF. The number (percentage) will be presented by treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Analysis Sets will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, BMI, waist circumference, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit character code using the World Health Organization Drug Dictionary (WHO DD) (01 Mar 2015). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started on or after the date of the dosing of study drug and continued up to 30 days afterward. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

For the primary and secondary endpoints, a 2-sided α=0.05 significance level will be used.

The primary analysis is:

- The proportion of subjects achieving ≥5% BMI reduction will be analyzed using logistic regression model with treatment and site as factors and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 52, as nonresponders (did not achieve ≥5% BMI reduction).

The secondary analyses are:

- The proportion of subjects achieving ≥5% BMI reduction will be analyzed using logistic regression model with treatment and site as a factors, and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 12. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 12, as nonresponders (did not achieve ≥5% BMI reduction).
- Change and percent change from baseline in BMI will be analyzed using an analysis of covariance model with treatment and site as factors and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52 using the last observation carried forward (LOCF) approach. The FAS analysis set will be used for this analysis. Additional sensitivity analyses will be performed using model-based imputation methods that will be described separately in the SAP.
- Rates of growth in height will be summarized by the height distribution of percent change from Baseline to Week 52 by treatment group. The Safety Analysis Set will be used for this analysis.
- Tanner Staging (II, III, IV, and V) will be summarized using shift tables from Baseline to Week 52 by treatment group. The Safety Analysis Set will be used for this analysis.

- C-SSRS: The incidence of suicidal ideation or suicidal behavior will be summarized by treatment groups. The Safety Analysis Set will be used for this analysis.
- The change from baseline for the endpoints HbA1c, fasting plasma glucose, fasting insulin, HOMA-IR, waist circumference, blood pressure (systolic and diastolic), and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) will be analyzed using a mixed-effects model with repeated measures with treatment and site as factors and baseline as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis.
- The proportion of subjects achieving ≥10% BMI reduction will be analyzed using logistic regression model with treatment and site as factors, and baseline BMI as a covariate. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for this analysis. Sensitivity analysis will be conducted treating subjects with missing BMI data at Week 52 as nonresponders (did not achieve ≥10% BMI reduction).
- A logistic regression model with treatment and site as factors will be used to analyze the following endpoints. Comparison between BELVIQ and placebo will be made at Week 52. The FAS analysis set will be used for these analyses. Sensitivity analysis will be conducted using LOCF for subjects with missing data at Week 52.
    - Proportion (%) of subjects with confirmed pre-hypertension or primary hypertension
    - Proportion (%) of subjects with dyslipidemia
    - Proportion (%) with metabolic syndrome that met at least 2 IDF criteria

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. The effect of covariates, such as baseline characteristics/demographics, on PK will be explored. Derived exposure parameters such as the maximum observed concentration (C_{max}) and the area under the concentration-time curve from time zero to 24 hours at steady-state ($AUC_{0\text{-}24,ss}$) will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history. The PK analysis set will be used for this analysis.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Proportion (%) of patients achieving ≥5% and ≥10% BMI reduction, and BMI change from baseline will be assessed as the PD analysis. The PD analysis set will be used for this analysis.

Other assessments (ie, BMI change, percentage of BMI change, proportion [%] of patients achieving ≥10% BMI reduction, and waist circumference from baseline) will also assessed as PD analysis. The PK/PD analysis set will be used for this analysis.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Population PK/PD modeling will be used to explore the relationship between exposure to BELVIQ and response, including but not limited to change in BMI from baseline and the probability of achieving ≥5% and ≥10% change in BMI from baseline to Week 52. Additionally, exposure-safety relationships for select safety parameters may be explored graphically. Any emergent relationship may be modeled as appropriate. Any parameters based on the study data may be considered for exploratory assessment for its relationship to PK.

9.7.1.7.4 PHARMACOGENOMIC AND PHARMACOGENETIC ANALYSES

At the time of randomization, when applicable, a blood sample will be taken for potential investigation of genetic variability associated with genotypes relating to response to BELVIQ, weight loss, susceptibility to diabetes, and their associated risk factors (Appendix 3).

Data obtained from the PD and PG samples will be used for research. The PD and PGsamples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to BELVIQ and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for re-consenting and the sample will be destroyed

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical examination), suicidal ideation/behavior (C-SSRS), neuropsychiatric events, out-of-normal-range laboratory safety test variables, along with change from baseline in laboratory safety test variables, and vital sign measurements at end of treatment will be summarized by treatment group using descriptive statistics. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Subjects will receive BELVIQ 20 mg or placebo QD for up to 52 weeks.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by treatment group and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by day and time after dosing.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Bazett and QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

QTc interval >450 ms

QTc interval >480 ms

QTc interval >500 ms

Change from baseline in QTc interval:

QTc interval increases from baseline >30 ms

QTc interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable

9.7.2 Determination of Sample Size

A sample size of 360 subjects in a 1:1 ratio (n=180 in the BELVIQ 20 mg QD treatment group: n=180 in the placebo group) will have 90% power to detect a 20% difference in proportions of subjects with at least 5% reduction in BMI, assuming the placebo response is 20%, using a 2-sided test and α=0.05, assuming a 35% dropout rate. The assumption is based on lorcaserin adult Phase 3 and adolescent studies with orlistat and sibutramine (Chanoine JP, 2005; Berkowitz. R, 2006).

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. Investigational product will be stored in accordance with the DEA Regulations for Scheduled III - V Drugs and labeled storage conditions. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDIX

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Family-Based Lifestyle Program

Program Overview

All subjects and their caregivers (participating parent/guardian) in Study 403 will participate in a standardized weight management program for adolescents consisting of multicomponent behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight-loss maintenance. The role of the caregivers is to support their adolescents' lifestyle changes and their taking of study medication.

The objectives of this program are as follows:

- Develop a weight management program for all BELVIQ study participants and their caregivers (caregivers are instructed in methods to support their adolescents' progress but caregivers are themselves not instructed to lose weight or take medication)
- Standardize the weight management program across all study sites
- Maximize participant retention
- Promote participant's adherence to both taking study medication and following the lifestyle program

Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), pharmacogenomic (PG), and other biomarker analysis. These samples may be used for discovery or validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the PD, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PG, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BELVIQ® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/BELVIQ® (lorcaserin hydrochloride)
IND Number:	069888

SIGNATURES

Authors:

PPD

Date

Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

PPD

Date

Eisai Inc.

PPD

Date

Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	APD356-A001-403
Study Protocol Title:	A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BELVIQ® in Conjunction with Lifestyle Modification for Weight Loss in Obese Adolescents, Age 12 to 17 Years
Investigational Product Name:	APD356/BELVIQ® (lorcaserin hydrochloride)
IND Number:	069888

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date