STATISTICAL ANALYSIS PLAN

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
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BOCF	baseline observation carried forward
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
EOS	end of study
EOT	end of treatment
FAS	full analysis set
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
LDL	low density lipoprotein
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model repeated measurement analysis
PD	pharmacodynamics
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PP	per-protocol analysis set
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Abbreviation	Term
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol APD356-A001-403.

Since this study has been terminated early and when only about 20% of subjects have completed week 52 visit, many of the planned efficacy outputs will not show enough data as initially planned for this study. Most planned efficacy tables will not be produced. For details on changes in planned analysis, please see section 7 "Changes in Planned Analysis".

This document is prepared based on the final study protocol (protocol V10.0 12Feb2018). Reader is referred to the final study protocol, the case report form (CRF), general CRF completion guidelines for details of study design, conduct and data collection.

3.1 Study Objectives

3.1.1 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 QD as compared to placebo

3.1.2 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

3.1.3 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 (e.g., 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

- 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

- Effects on body fat and lean mass composition by Dual-energy X-ray Absorptiometry (DEXA) in a subset of randomized subjects (selected prior to randomization) at selected sites during 52 weeks of

- Changes in cardiovascular risk factors associated with obesity (e.g., 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

- 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.

- To assess the pharmacokinetic (PK) of lorcaserin using population PK modeling

- To assess relationships between plasma exposure to lorcaserin and pharmacodynamics (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

3.2 Overall 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 (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. 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.

Details of the study procedures and schedule of assessments can be found in Table 2 of the protocol.

4 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/m2 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/m2 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)

5 STATISTICAL METHODS

Descriptive statistics will be reported for continuous variables using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using frequency count as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

- Change in BMI from Baseline to Week 52

5.1.2 Secondary Endpoints

KEY SECONDARY ENDPOINT

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

OTHER SECONDARY 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 HbA1c 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 treatment (per Amendment 03)

5.2 Study Subjects

5.2.1 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 post dose safety assessment.

The Full Analysis Set (FAS) is the group of all randomized subjects who received at least 1 dose of study drug.

PK Analysis Set: the PK analysis set is the group of subjects who have at least 1 quantifiable plasma concentration of lorcaserin with adequately documented dosing history.

The number (percentage) of subjects in each analysis set will be summarized by treatment groups using descriptive statistics.

5.2.2 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.

5.2.3 Protocol Deviations

Major protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unbinding. All protocol deviations will be categorized according to standard classifications including the following:

- Violations of inclusion/exclusion criteria

- Noncompliance with protocol procedures/assessments
- Noncompliance of drug dosage
- Use of prohibited treatments

All significant protocol deviations will only be presented in the listings.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis set will be summarized for each treatment group and overall using descriptive statistics or frequency count. Continuous variables include age, weight, height, body mass index (BMI) and waist circumference; categorical variables include age group, sex, ethnicity, and race.

MEDICAL HISTORY

All medical histories as documented by the Investigator will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number (percentage) of subjects reporting a history of any medical condition, as recorded on CRF, will be summarized by System Organ Class (SOC), preferred term for each treatment group and overall based on FAS.

5.2.5 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).

Prior medications are defined as medications that stop prior to the first dose of study drug. Concomitant medications are defined as medications that (1) start before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) start on or after the date of the first dose of study drug, up to 30 days after the last dose of study drug.

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 WHO DD preferred term (PT). If a subject takes the same medications for the same class level or drug name, the subject will be counted only once for that class level or drug name.

5.2.6 Treatment Compliance

Treatment compliance is defined as follows: Total number of tablets dispensed – total number of tablets lost or returned divided by total number of tablets subject should have taken.

Treatment compliance will be summarized using descriptive statistics by treatment group based on FAS and Safety Analysis Set. Treatment compliance will also be summarized by treatment group using the categories $<80\%$, $\geq 80\%$ to $\leq 100\%$, $>100\%$ to $\leq 120\%$, and $>120\%$.

5.3 Data Analysis General Considerations

The FAS will be used for all efficacy analyses, and since study has been terminated early, there will be no additional supportive or sensitivity analysis.

5.3.1 Pooling of Centers

No pooling of centers will be done since there will be no ANCOVA analysis.

5.3.2 Adjustments for Covariates

There will be no analysis of covariance and only basic summary of descriptive statistics will be performed for the BMI.

5.3.3 Multiple Comparisons/Multiplicity

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

5.3.4 Examination of Subgroups

Subgroup analyses will be performed on the primary efficacy endpoint using age group (<12, 12 - <13, 13 - <14, 14 - <15, 15 - <16, 16 - <17, 17 - <18 and > 18 yrs.), sex (male and female), race (white, black, Asian, and other). Additional subgroup analysis may also be explored, if deemed appropriate.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Due to the early termination of the study, no imputation analysis will be performed.

5.3.6 Other Considerations

Due to the early termination of the study, only simple summary of descriptive statistics will be provided for efficacy endpoint.

Individual subject data in the database will be presented in data listings.

The following rules/definitions will be applied in the final outputs:

- Homeostatic Model Assessment of Insulin Resistance ((HOMA-IR Fasting insulin (mIU/L) x Fasting glucose (mmol/L) / 22.5)

- Dyslipidemia: Please use the following link: (https://www.nhlbi.nih.gov/files/docs/peds_guidelines_sum.pdf) and consider subject "with Dyslipidemia" if TC ≥ 170 or LDL-C ≥ 110 or Non- HDL-C ≥ 120 or TG ≥ 90 or HDL-C ≤ 40. Values given are in mg/dL. ***To convert to SI units****, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density*

lipoprotein cholesterol (HDL-C), and non-HDL-C by 38.6; for triglycerides (TG), divide by 88.6.

- Prehypertension or Hypertension:

  BP is classified as SBP and DBP percentiles for age/sex/height.
  Prehypertension: If SBP or DBP ≥ 90th percentile or < 95th percentile or BP >120/80 mmHG to < 95th percentile
  Hypertension: If SBP or DBP ≥ 95th percentile or BP ≥ 95th percentile

- Subjects who are type 2 diabetes (T2DM) at Baseline are defined as follows:

  Positive diagnosis of diabetes (Preferred Term: *Type 2 diabetes mellitus*) based on Medical History Form or AE with the start date prior to the first dose of the study drug.

The formula for BMI is weight in kilograms divided by height in meters squared.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), minimum value (min), and maximum value (max). Minimum and maximum values will be reported with the same precision as the units of measure. The mean and median will be reported to 1 greater decimal place, and the SD will be reported to 2 additional decimal places.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline Value: The baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the initial administration of study drug. Unscheduled visit measurements will be included for derivation of baseline.

Change (Absolute Change) from baseline: will be calculated as Post baseline value - Baseline value.

Percent change from baseline: will be calculated and expressed in percentages as 100×(Post baseline value - Baseline value)/Baseline value.

Unscheduled Visits: Unscheduled visit measurements will be included in listings, for derivation of visit windows and computation of baseline/last on-treatment visit.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

5.4 Efficacy Analyses

The FAS will be used as the primary population for the efficacy analyses. Due to the early termination of the study, only summary of descriptive statistics will be presented for efficacy variables.

5.4.1 Primary Efficacy Analyses

Due to the early termination of the study, only summary of descriptive statistics will be presented.

Multiple Imputation

No multiple imputation will be performed.

5.4.1.2 Sensitivity Analysis

There will be no sensitivity analyses due to the early termination of the study.

5.4.1.3 Subgroup Analysis

Due to the early termination of the study, the analysis of following planned subgroups will not be performed:

- age group
- sex (male and female)
- race (white, black, Asian and other)
- BMI group

5.4.2 Key Secondary Efficacy Analyses

Due to the early termination of the study, only summary of descriptive statistics will be presented.

5.4.3 Other Secondary Efficacy Analyses

The following efficacy analyses are for exploratory purpose only. For each efficacy endpoint specified below, only basic summary of descriptive statistics will be presented.

5.4.3.1 Proportion of subjects achieving at least a 5% BMI reduction at Week 12

5.4.3.2 Proportion of subjects achieving at least a 10% BMI reduction at Week 52

5.4.3.3 Percent change in BMI from baseline at Week 52

5.4.3.4 Change and percentage change in BMI from Baseline to Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12

5.4.3.5 Proportion of subjects achieving at least a 5% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12

5.4.3.6 Proportion of subjects achieving at least a 10% BMI reduction at Week 52 by the outcome of achieving at least a 5% BMI reduction at Week 12

5.5 Pharmacokinetic, Pharmacodynamics, Pharmacogenomics, and Other Biomarker Analyses

The methodology for these analyses will not be included in this SAP but will be described in a separate analysis plan if deemed necessary.

5.5.1 Pharmacokinetic Analyses

Lorcaserin plasma concentration-time data will be summarized.

5.5.2 Pharmacodynamics, and Other Biomarker Analyses

No PK analysis will be performed. Only lorcaserin plasma concentration-time data will be summarized.

5.6 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, and 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. 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.
All safety analyses should be based on “as treated” groups.

5.6.1 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.

5.6.2 Adverse Events

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

5.6.3 Laboratory Values

Laboratory results will be summarized using standard international units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each post baseline 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 no missing baseline and relevant post baseline 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.

5.6.4 Vital Signs

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

In addition, clinically notable vital sign values will be identified using the criteria in Table 2. The clinically notable vital sign values will be summarized using frequency count at each visit by treatment group.

Table 2 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Pulse rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L
Weight	--	Increase of ≥7%	H
	--	Decrease of ≥7%	L
Respiratory Rate	>20 bpm	--	H
	< 10 bpm	--	L

BP = blood pressure, H = high, L = low.

a. Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

5.6.5 Electrocardiograms

For each ECG parameter (including PR interval, RR interval, QRS interval, QT interval, QTc interval (Bazett formula), QTc interval (Fridericia formula), 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 post baseline QTc (Bazett) and QTc (Fridericia) will also be tabulated by treatment group as follows:

- Number (percentage) of subjects with
- 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.

5.6.6 Other Safety Analyses

Other safety analyses will include the following:

- Change in puberty status
- Waist circumference
- DEXA Z-score
- Cognition
- Depression
- Valvular function
- Pulmonary pressures

6 INTERIM ANALYSES

"No interim analyses are planned for this study."

7 CHANGES IN THE PLANNED ANALYSES

Due to the early termination of the study, the following changes are made from the initial planning for the study:

1. There will be no ANCOVA or MMRM analysis for any of the efficacy endpoints. Only basic summary of descriptive statistics will be presented.

2. All secondary endpoint analysis of type 2 diabetes will not be provided since there is only 1 subject of type 2 diabetes.

3. All planned supportive and sensitivity analysis (MMRM, MNAR imputation, per protocol) will not be performed.

4. Summary of major protocol deviation will not be performed and only data listing will be presented.

5. No subgroup analysis will be performed for the primary endpoint analysis.

8 HANDLING OF MISSING DATA, DROP-OUTS, AND OUTLIERS

For determining treatment emergent markedly abnormal lab values, a missing baseline lab value will be assumed to be of grade 0.

No special handling of missing data is planned for the analysis of any of the efficacy or safety variables.

8.1.1 Visit Windowing

Table 1 will be applied to all measurements including those from unscheduled visits and early termination visits to attain the measurement for analysis for the given scheduled visit.

Table 1 Windowing Rules for Safety Endpoints

Visit	Target Visit Day (in study days)	Visit Window (in study days)
Week 0	Day 1	Day 1
Week 1	7	2-21
Week 5	35	22-45
Week 8	56	46-70
Week 12	84	71-112
Week 20	140	113-168
Week 28	196	169-224
Week 36	252	225-280
Week 44	308	281-336
Week 52	364	337-379
Week56/FU		>379 or analysis visit date > last dose date +14
EOT		For last non missing analysis visit date ≤ 379 or ≤ last dose date +14 days.

In case of multiple assessments within the same visit window, the assessment closest to the target visit day will be used in data analyses; in the event of two assessments being equally close to the scheduled visit day, the latest assessment in the sequence will be used.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or later versions).

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and graphs shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. American Diabetes Association. Standards of Medical Care - 2013. Diabetes Care 2013; 36 Suppl 1:S11-S66.
2. Children and Adolescents: Summary Report Pediatrics. 2011; 128:S213-S256.
3. FDA CDER Division of Metabolic and Endocrine Drug Products (HFD - 510). 2003;
4. FDA CDER Division of Metabolic and Endocrine Drug Products (HFD - 510). 2007;

13 APPENDICES

13.1 Sponsor's grading for Determining Markedly Abnormal Laboratory Results

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 (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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences; seizures
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

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: 28 May 2009 (v4.03: 14 Jun, 2010).
ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, , LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.

SIGNATURE PAGE

Author(s):

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Date

Approval:

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Date

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