Clinical Trial Protocol AZP01-CLI-003

A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome

Investigational Product:	**Livoletide** (AZP-531)
Study Name:	ZEPHYR
Protocol Code Number:	AZP01-CLI-003
Development Phase:	Phase 2b/3
EudraCT number:	**2018-003062-13**
IND number:	130864
NCT number:	**03790865**
Trial Sponsor:	Millendo Therapeutics SAS 15G Chemin du Saquin Ecully 69130, France
Sponsor's Medical Officer:	**Soraya Allas, MD, PhD**
Current Protocol Version:	**1.2**
Date:	**July 31st, 2019**

STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with guidelines of International Council for Harmonisation Good Clinical Practice E6 (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and all applicable national and local regulatory requirements. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND)/Clinical Trial Authorization (CTA) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s), all recruitment materials, and all participant materials will be submitted to applicable IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the applicable IRB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

SPONSOR PROTOCOL APPROVAL

Protocol Title: *A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome*

Protocol Number: AZP01-CLI-003

Current Version: **1.2, July 31st, 2019**

I, the undersigned, have read this protocol and agree with its content and confirm that it contains all necessary information required to conduct the study.

Approved by:

Responsible Sponsor Medical Officer

Signature: _____ **Date:** July 31st, 2019

Soraya Allas, MD, PhD
Vice President, Clinical Development

INVESTIGATOR'S AGREEMENT

Protocol Title: *A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome*

Protocol Number: AZP01-CLI-003

Current Version: **1.2, July 31st, 2019**

I have carefully read Protocol AZP-CLI-003 entitled "A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome".

I confirm that I have read and agree to conduct the clinical study as outlined in the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki as amended, and all other applicable regulatory requirements. Furthermore, I understand that the Sponsor, Millendo Therapeutics SAS, and the Institutional Review Board/Research Ethics Board/Ethics Committee (IRB/REB/EC) must approve any changes to the protocol in writing before implementation.

I agree on behalf of myself and all other personnel involved in the clinical study who are employed by me, to maintain confidentiality of all information received or developed in connection with this protocol. All data pertaining to this study will be provided to Millendo Therapeutics and any presentation or publication of study data will be reviewed by Millendo Therapeutics, before release.

I have read and agree to the following Confidentiality Statement:

Confidentiality Statement: This protocol and any related documents from Millendo Therapeutics, contain privileged information that is confidential and may not be disclosed unless such disclosure is required by federal laws or regulations. In any event, persons to whom the information is disclosed must be informed that it is privileged and/or confidential and may not be further disclosed by them. Information from this study may not be reproduced in any form without the written permission of Millendo Therapeutics.

PRINCIPAL INVESTIGATOR:

_____ _____

Principal Investigator's Signature Date

_____

Print Principal Investigator's Address and Telephone Number

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SERIOUS ADVERSE EVENTS REPORTING

CRO Safety Department: Medpace Clinical Safety

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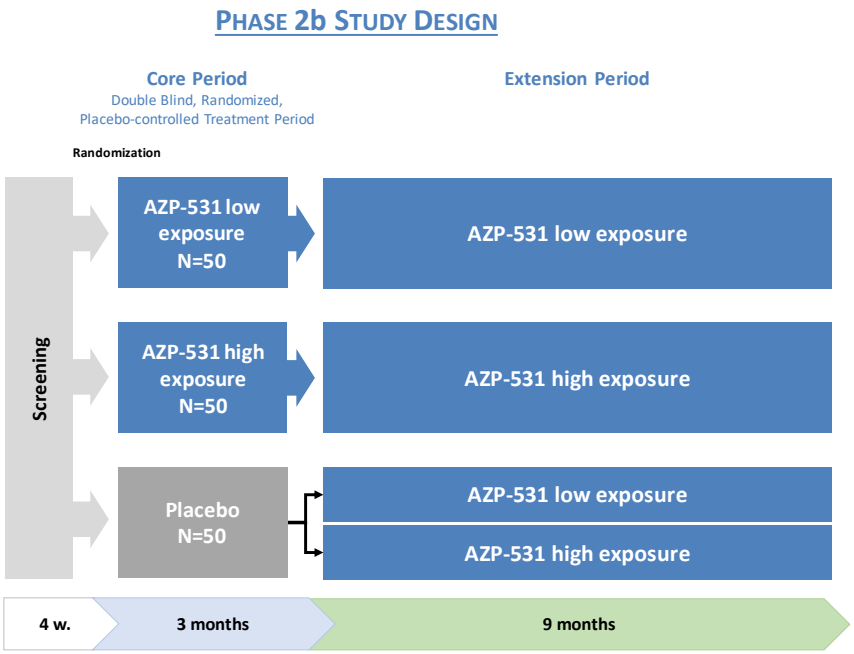
Table of Contents

1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor:	Millendo Therapeutics SAS 15G Chemin du Saquin Ecully 69130, France
Name of Investigational Product:	Livoletide (formerly known as AZP-531)
Title of Study:	A Phase 2b/3 study to evaluate the safety, tolerability, and effects of Livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome
Study name:	ZEPHYR
Sponsor Protocol Number:	AZP01-CLI-003
Phase of Development:	2b/3
Study Centers:	Approximately 40 sites in Europe, Australia and North America
Indication:	Hyperphagia and food-related behaviors in patients with Prader-Willi syndrome (PWS)
Study Design:	This protocol includes 2 consecutive parts: 1. The first part is a Phase 2b dose-response study consisting of a 3-month double-blind, placebo-controlled Core Period and a 9-month Extension Period. 2. The second part is a Phase 3 study consisting of a 6-month double-blind, placebo-controlled Core Period followed by a 6-month Extension Period. Phase 3 may be initiated following review of safety and efficacy results at the completion of the Phase 2b Core Period. Patients who enrolled in the Phase 2b part will not be eligible for recruitment in the Phase 3 part. **Phase 2b** Phase 2b will include: • A 3-month, double-blind, randomized, placebo-controlled treatment period (Phase 2b Core Period). After a screening period (up to 4 weeks), eligible patients will be randomized in a 1:1:1 ratio to one of two livoletide doses (8 mg/mL, low exposure or 16 mg/mL, high exposure) or placebo. Randomization will be stratified based on age (≥4 and < 8 years of age, ≥8 and <18 years of age and ≥18 years of age) and body mass index (BMI) (patients ≥18 years of age: BMI <27 kg/m^2 vs BMI ≥27 kg/m^2; patients 4-17 years of age: BMI <90th percentile vs BMI ≥90th percentile for the same age and sex); • A 9-month Extension Period (Phase 2b Extension Period). Patients randomized to livoletide for the Core Period will remain on the randomized dose (i.e. 8 mg/mL, low exposure or 16 mg/mL, high exposure) during the Extension Period. Patients randomized to placebo for the Core Period will cross-over to livoletide low or high exposure in a randomized (1:1) manner. The Interactive Response Technology (IRT) will manage treatment assignment so that the double-blind status can remain intact at the start of the Extension Period.

Study Design Continued:



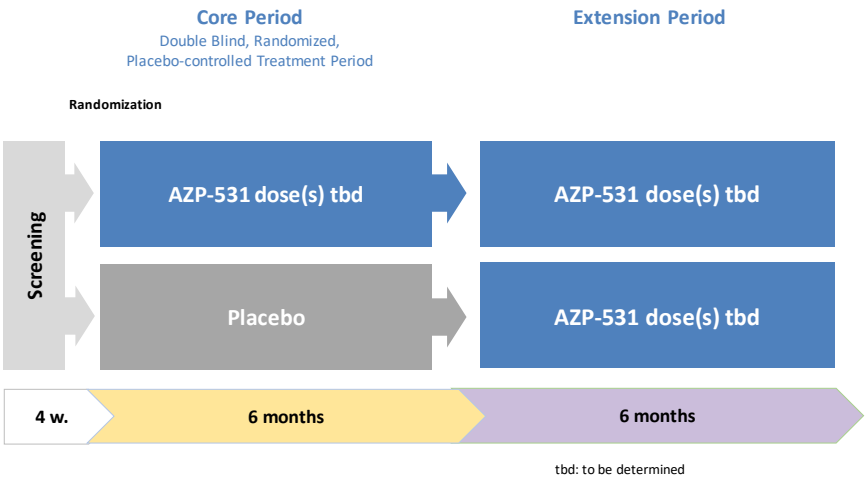
Abbreviations: AZP-531=livoletide; N=number of patients; w=weeks.

Phase 3

Phase 3 may commence after completion of the Phase 2b Core Period. Following review of data at the completion of the Phase 2b Core Period, the Phase 3 livoletide doses will be reassessed along with the statistical assumptions. Patients who enrolled in the Phase 2b part will not be eligible for recruitment in the Phase 3 part.

Phase 3 will include:

- A 6-month, double-blind, randomized, placebo-controlled treatment period (Phase 3 Core Period). After a screening period (up to 4 weeks), eligible patients will be randomized to livoletide or placebo;
- A 6-month Extension Period (Phase 3 Extension Period). Patients randomized to livoletide for the Core Period will remain on the randomized dose during the Extension Period. Patients randomized to placebo for the Core Period will cross-over to livoletide during the Extension Period. The IRT will manage treatment assignment so that the double-blind status can remain intact at the start of the Extension Period.

Study Design Continued:	**PHASE 3 STUDY DESIGN**  Abbreviations: AZP-531=livoletide; tbd=to be determined; w=weeks.
Objectives:	**<u>Phase 2b</u>** **PHASE 2b CORE PERIOD** **Primary efficacy objective:** To demonstrate the efficacy of a 3-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by the Hyperphagia Questionnaire for Clinical Trials (HQ-CT). **Secondary efficacy objectives:** • To demonstrate the efficacy of 3-month treatment with livoletide as compared to placebo for: – Reducing total body fat mass in overweight/obese patients with PWS; – Reducing waist circumference (WC) in overweight/obese patients with PWS; – Reducing body weight (BW) in overweight/obese patients with PWS. **Safety objective:** • To assess the safety and tolerability of livoletide as compared to placebo over a 3-month treatment period. **Pharmacokinetic objective:** • To characterize the plasma pharmacokinetic (PK) of livoletide in patients with PWS; **Additional assessments:** • To evaluate the effect of livoletide as compared to placebo on: – Hyperphagia severity as assessed by the Caregiver and Clinical Global Impression of Severity - Hyperphagia scales (CgGIS-H and CGIS-H, respectively); – Hyperphagia global impression of change as assessed by the Caregiver and Clinical Global Impression of Change - Hyperphagia scales (CgGIC-H and CGIC-H, respectively); – Clinical global impression of change as assessed by the Clinical Global Impression of Improvement (CGI-I) scale;

Objectives Continued:	– Clinical global impression of severity as assessed by the Clinical Global Impression of - Severity (CGI-S) scale; – Fasting (for approximately 8 hours) and postprandial glucose and insulin (profile); – Patient-reported appetite following breakfast as assessed by a Numeric Rating Scale (NRS); – Patients' Non-Food-Related behavior as assessed by the Developmental Behavior Checklist 2-Parent/Carer version (DBC2-P); – Patients' Quality of Life (QoL) as assessed by the Pediatric Quality of Life inventory™ (PedsQL™) 4.0 Generic Core Scales; – Caregivers' disease burden as assessed by the Zarit Burden Interview (ZBI); – Health state utilities as assessed by European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L) Self-complete version and Proxy version 1; • To evaluate the measurement properties of HQ-CT in the study population (test-retest reliability, construct validity and ability to detect change); • To derive the responder threshold for meaningful change in the HQ-CT; • To compare the percentage of HQ-CT responders between groups. **PHASE 2b EXTENSION PERIOD** **Efficacy objectives:** • To assess the maintenance of efficacy of livoletide treatment on caregiver-observed food-related behavior as assessed by the HQ-CT; • To assess the maintenance of efficacy of livoletide treatment on total body fat mass, WC, and BW in overweight/obese patients with PWS. **Safety objective:** • To assess the long-term safety and tolerability of livoletide over a 12-month treatment period. **Pharmacokinetic objective:** • To characterize the plasma PK of livoletide in patients with PWS; • To characterize the plasma PK profile of livoletide in a subset of patients with PWS. **Additional assessments:** • To evaluate the long-term effects of livoletide on: – Hyperphagia severity as assessed by the CgGIS-H and CGIS-H; – Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H; – Clinical global impression of change as assessed by the CGI-I; – Clinical global severity as assessed by the CGI-S; – Fasting (for approximately 8 hours) glucose and insulin; – Patients' Non-Food-Related behavior as assessed by the DBC2-P version; – Patients' QoL as assessed by the PedsQL™ 4.0 Generic Core Scales; – Caregiver disease burden as assessed by the ZBI; – Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1.

Objectives Continued:	**Phase 3:** **PHASE 3 CORE PERIOD** **Primary efficacy objective:** To demonstrate the efficacy of a 6-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by HQ-CT. **Secondary efficacy objectives:** • To demonstrate the efficacy of 6-month treatment with livoletide as compared to placebo for: – Reducing total body fat mass in overweight/obese patients with PWS; – Reducing WC in overweight/obese patients with PWS; – Reducing BW in overweight/obese patients with PWS. **Safety objective:** • To assess the safety and tolerability of livoletide as compared to placebo over a 6-month treatment period. **Additional assessments:** • To evaluate the effect of livoletide as compared to placebo on: – Hyperphagia severity as assessed by the CgGIS-H and CGIS-H; – Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H; – Clinical global impression of change as assessed by the CGI-I; – Clinical global impression of severity as assessed by the CGI-S; – Fasting (for approximately 8 hours) and postprandial glucose and insulin (profile); – Patient-reported appetite following breakfast as assessed by NRS; – Patients' Non-Food-Related behavior as assessed by the DBC2-P; – Patients' QoL as assessed by the PedsQL™ 4.0 Generic Core Scales; – Caregivers' disease burden as assessed by the ZBI; – Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1; • To compare the percentage of HQ-CT responders between groups. **PHASE 3 EXTENSION PERIOD** **Efficacy objectives:** • To assess the maintenance of efficacy of livoletide treatment on caregiver-observed food-related behavior as assessed by the HQ-CT; • To assess the maintenance of efficacy of livoletide treatment on total body fat mass, WC, and BC in overweight/obese patients with PWS. **Safety objective:** • To assess the long-term safety and tolerability of livoletide over a 12-month treatment period.

Objectives Continued:	**Additional assessments:** • To evaluate the long-term effects of livoletide on: – Hyperphagia severity as assessed by the CgGIS-H and CGIS-H; – Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H; – Clinical global impression of change as assessed by the CGI-I; – Clinical global severity as assessed by the CGI-S; – Fasting (for approximately 8 hours) glucose and insulin; – Patients' Non-Food-Related behavior as assessed by the DBC2-P version; – Patients' QoL as assessed by the PedsQL™ 4.0 Generic Core Scales; – Caregiver disease burden as assessed by the ZBI; – Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1.
Number of patients (planned):	For **Phase 2b**, a total of approximately 50 patients per group (8 to 65 years of age) will need to be randomized (approximately 150 patients in total). In addition to this cohort of 150 patients, a separate cohort of patients 4 to 7 years of age will also be randomized to one of the 3 arms. For **Phase 3**, the total number of required patients to be randomized is estimated to be 50 patients per group. Final sample size will be determined following analysis of data at the completion of the Phase 2b Core Period.
Duration of Study Participation:	The overall study duration for each patient in both Phase 2b and Phase 3, inclusive of screening and follow-up, will be approximately 14 months.
Diagnosis and Main Eligibility Criteria for Inclusion:	**<u>Phase 2b</u>** **PHASE 2b INCLUSION CRITERIA (CORE PERIOD)** To be enrolled in the study, patients must meet all the following criteria at screening: 1. A confirmed genetic diagnosis of PWS. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If the PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria. 2. Male and female patients 4 to 65 years of age, inclusive, 12 to 65 years of age for Australian sites 201 and 202. 3. Have evidence of increased appetite or hyperphagia, as judged by the investigator, and a total HQ-CT score ≥10 (scale of 0-36). 4. Patients willing to comply with the following lifestyle considerations: a. Be on a stable diet regimen. b. Be on a stable physical activity regimen. Patients should agree to refrain from changing their usual level of physical activity. 5. Each patient must have a single primary caregiver who will be able to evaluate and score that patient's behaviors and perform any study-related activities as defined in the protocol throughout the study. That person must have been caring for the patient for at least 6 months prior to screening, spend, on average, approximately 4 (or more) waking hours per day with the patient, and should be available for the duration of the study.

Diagnosis and Main Eligibility Criteria for Inclusion: Continued:	a. During the Extension Period, the time spent by the caregiver with the patient may be reduced, as long as the caregiver spends, on average, approximately 4 (or more) waking hours per day with the patient at least 2 weeks before each visit. 6. BMI ≤65 kg/m^2 for adult patients. 7. Women of Child Bearing Potential (WCBP) must have a negative pregnancy test. 8. All WCBP, sexually active male patients, and all opposite sex partners of patients should agree to use medically-approved effective methods of birth control (e.g. diaphragm, condoms with spermicide) throughout the study and for 30 days after the last dose of study drug. a. WCBP or male patients who agree with a true abstinence (when in line with the preferred or usual lifestyle of the patient) can be included. 9. Adequate renal function, defined as serum creatinine ≤1.5 × upper limit of normal (ULN). 10. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤3 × ULN. 11. Diabetes medications will be permitted if doses have been stable for at least 3 months prior to screening. Insulin doses are considered to have been stable if the prescribed total daily insulin doses are within approximately 20% of those at screening. 12. Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening. 13. Psychotropic treatment (e.g. modafinil, topiramate, zonisamide, fluoxetine, aripiprazole, risperidone, quetiapine, and benzodiazepines) will be permitted if doses have been stable for at least 2 months prior to screening. 14. Any other medication that is likely to affect behavior, body composition, or lipids (in the opinion of the investigator) must be stable for at least 2 months prior to screening, except as noted below: a. Thyroid hormone: changes within approximately 13 µg/day are acceptable b. Sex steroids: patients on sex steroids must have been taking them for at least 2 months at screening; dose changes within approximately 25% of the screening dose are acceptable as are changes within a class (e.g., from one oral contraceptive to another, or from one selective estrogen receptor to another). 15. Approved informed consent (Assent form for patients under the age of majority), signed by the patient, parent, or legal guardian, as appropriate, at the screening visit before any study procedures. 16. For patients **from France only**: Is either affiliated with or a beneficiary of "sécurité sociale". **PHASE 2b EXCLUSION CRITERIA (CORE PERIOD)** A patient will be excluded if they meet any of the following criteria at screening: 1. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspected alcohol abuse. 2. History of significant cardiovascular disease including history of congestive heart failure (CHF, New York Heart Association [NYHA] Class 3 or 4), angina pectoris, or myocardial infarction (MI) within 6 months prior to screening.

Diagnosis and Main Eligibility Criteria for Inclusion: Continued:	3. Type 1 diabetes mellitus. 4. Glycated hemoglobin (HbA1c) >10%. 5. History of frequent hypoglycemia. 6. Blood pressure systolic >160 mmHg, diastolic >90 mmHg (adult patients) and blood pressure systolic >140 mmHg, diastolic >90 mmHg (patients 4 to 17 years of age). 7. Use of weight loss agents and medications taken to affect appetite (e.g. Orlistat®, Lorcaserin, Qsymia®, Contrave®/Mysimba®, glucagon-like-peptide 1 [GLP-1] analogs, as well as any over-the counter medication and herbal agent) within 2 months prior to screening. 8. Co-morbid condition or disease (such as respiratory disease or psychiatric disorder) diagnosed less than 1 month prior to screening. 9. Co-morbid condition or disease or abnormal laboratory finding that would in the investigator's judgment increase the patient risk to participating in this study or that will not allow the patient to complete the study. 10. Known history of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). 11. Participation in a clinical trial with an investigational agent within 3 months prior to screening. 12. Clinically significant abnormalities on electrocardiogram (ECG) at screening, as follows: a. Patients 4 years of age: males QT interval corrected for heart rate by Bazett's formula (QTcB) >448 ms, females QTcB >442 ms. b. Patients 5 to 7 years of age: males QTcB >443 ms, females QTcB >449 ms. c. Patients 8 to 11 years of age: males QTcB >440 ms, females QTcB >447 ms. d. Patients 12 to 15 years of age: males QTcB >449 ms, females QTcB >457 ms. e. Patients ≥16 years of age: males QTcB >450 ms, females QTcB >470 ms. 13. Pregnant or lactating woman. 14. History of hypersensitivity to drugs with a similar chemical structure or class as livoletide (acylated ghrelin [AG] and unacylated ghrelin [UAG]). 15. Unwillingness or inability to follow the procedures outlined in the protocol. 16. Patients living in a group home ≥50% of the time. 17. Patients with body weight <20 kg. **EXTENSION PERIOD:** In order to be able to participate in the Extension Period, patients will be required to have completed the Core Period. **Phase 3** **PHASE 3 INCLUSION CRITERIA (CORE PERIOD)** To be enrolled in the study, patients must meet all the following criteria at screening: 1. A confirmed genetic diagnosis of PWS. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria. 2. Male and female patients 8 to 65 years of age, inclusive.

Diagnosis and Main Eligibility Criteria for Inclusion: Continued:	3. Have evidence of increased appetite or hyperphagia, as judged by the investigator, and a total HQ-CT score ≥10 (scale of 0-36). 4. Patients willing to comply with the following lifestyle considerations: a. Be on a stable diet regimen. b. Be on a stable physical activity regimen. Patients should agree to refrain from changing their usual level of physical activity. 5. Each patient must have a single primary caregiver who will be able to evaluate and score that patient's behaviors and perform any study-related activities as defined in the protocol throughout the study. That person must have been caring for the patient for at least 6 months prior to screening, spend, on average, approximately 4 (or more) waking hours per day with the patient, and should be available for the duration of the study. a. During the Extension Period, the time spent by the caregiver with the patient may be reduced, as long as the caregiver spends, on average, approximately 4 (or more) waking hours per day with the patient at least 2 weeks before each visit. 6. BMI ≤65 kg/m^2 for adult patients. 7. WCBP must have a negative pregnancy test. 8. All WCBP, sexually active male patients, and all opposite sex partners of patients should agree to use medically-approved effective methods of birth control (e.g. diaphragm, condoms with spermicide) throughout the study and for 30 days after the last dose of study drug. a. WCBP or male patients who agree with a true abstinence (when in line with the preferred or usual lifestyle of the patient) can be included. 9. Adequate renal function, defined as serum creatinine ≤1.5 × ULN. 10. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN and AST and ALT levels ≤3 × ULN. 11. Diabetes medications will be permitted if doses have been stable for at least 3 months prior to screening. Insulin doses are considered to have been stable if the prescribed total daily insulin doses are within approximately 20% of those at screening. 12. Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening. 13. Psychotropic treatment (e.g. modafinil, topiramate, zonisamide, fluoxetine, aripiprazole, risperidone, quetiapine, and benzodiazepines) will be permitted if doses have been stable for at least 2 months prior to screening. 14. Any other medication that is likely to affect behavior, body composition, or lipids (in the opinion of the investigator) must be stable for at least 2 months prior to screening, except as noted below: a. Thyroid hormone: changes within approximately 13 µg/day are acceptable b. Sex steroids: patients on sex steroids must have been taking them for at least 2 months at screening; dose changes within approximately 25% of the screening dose are acceptable as are changes within a class (e.g., from one oral contraceptive to another, or from one selective estrogen receptor to another). 15. Approved informed consent (Assent form for patients under the age of majority) signed by the patient, parent, or legal guardian, as appropriate, at the screening visit before any study procedures.

Diagnosis and Main Eligibility Criteria for Inclusion: Continued:	16. For patients **from France only**: Is either affiliated with or a beneficiary of "sécurité sociale". **PHASE 3 EXCLUSION CRITERIA (CORE PERIOD)** **A patient who enrolled in the Phase 2b part is not eligible for recruitment in the Phase 3 part.** A patient will be excluded if they meet any of the following criteria at screening: 1. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspected alcohol abuse. 2. History of significant cardiovascular disease including history of CHF (NYHA Class 3 or 4), angina pectoris, or MI within 6 months prior to screening. 3. Type 1 diabetes mellitus. 4. HbA1c >10%. 5. History of frequent hypoglycemia. 6. Blood pressure systolic >160 mmHg, diastolic >90 mmHg (adult patients), and blood pressure systolic >140 mmHg, diastolic >90 mmHg (patients 8 to 17 years of age). 7. Use of weight loss agents and medications taken to affect appetite (e.g. Orlistat®, Lorcaserin, Qsymia®, Contrave®/Mysimba®, GLP-1 analogs, as well as any over-the counter medication and herbal agent) within 2 months prior to screening. 8. Co-morbid condition or disease (such as respiratory disease or psychiatric disorder) diagnosed less than 1 month prior to screening. 9. Co-morbid condition or disease or abnormal laboratory finding that would in the investigator's judgment increase the patient risk to participating in this study or that will not allow the patient to complete the study. 10. Known history of hepatitis B, hepatitis C, or HIV. 11. Participation in a clinical trial with an investigational agent within 3 months prior to screening. 12. Patients who participated in the Phase 2b part of the study. 13. Clinically significant abnormalities on ECG at screening, as follows: a. Patients 8 to 11 years of age: males QTcB >440 ms, females QTcB >447 ms. b. Patients 12 to 15 years of age: males QTcB >449 ms, females QTcB >457 ms. c. Patients ≥16 years of age: males QTcB >450 ms, females QTcB >470 ms. 14. Pregnant or lactating woman. 15. History of hypersensitivity to drugs with a similar chemical structure or class as livoletide (AG and UAG). 16. Unwillingness or inability to follow the procedures outlined in the protocol. 17. Patients living in a group home ≥50% of the time. 18. Patients with body weight <20 kg. **EXTENSION PERIOD:** In order to be able to participate in the Extension Period, patients will be required to have completed the Core Period. Based on results from Phase 2b, some inclusion criteria for the Phase 3 Core and Extension Periods may be adjusted.

Dosage, Form, and Route of Administration for Livoletide:

Livoletide will be administered by subcutaneous (SC) injection at rotating sites on the abdomen. Livoletide must be kept refrigerated at 2 to 8°C (36 to 46°F).

The inclusion criterion age range of 4 to 65 years is expected to correspond to a BW range of ~20 to 140 kg. Therefore, livoletide will be dosed according to BW on a µg/kg basis and will be provided as a sterile liquid formulation (in 0.9% sodium chloride [NaCl] solution) in single-use clear glass vials. Two concentrations of livoletide will be available for this study, 8 mg/mL and 16 mg/mL. The volume of dosing will be adjusted according to BW (see table below) to achieve targeted livoletide exposure levels of approximately 60 µg/kg and 120 µg/kg (i.e. 8 mg/mL, low exposure or 16 mg/mL, high exposure).

	Low exposure (8 mg/mL)	**High exposure (16 mg/mL)**
Body weight range (kg)	**Daily injection volume (mL)**	**Daily injection volume (mL)**
20.0 to 29.0	0.125	0.125
30.0 to 49.0	0.250	0.250
50.0 to 70.0	0.375	0.375
>70.0	0.500	0.500

The exposure dosing will be adjusted if there is any weight change at the 3-month visit at the end of the Core Period in Phase 2b or at the 6-month visit at the end of the Core Period in Phase 3.

Reference Therapy, Dosage, and Mode of Administration:	Matching placebo to the livoletide study drug will be a 0.9% NaCl solution and will be provided as a sterile liquid formulation in single-use clear glass vials. Placebo will be administered at the same volume as livoletide by SC injection at rotating sites on the abdomen. Placebo must be kept refrigerated at 2 to 8°C (36 to 46°F).
Criteria for Evaluation:	**<u>Phase 2b</u>** **PHASE 2b CORE PERIOD** **Primary endpoint:** Change from baseline to the end of the 3-month Core Period for HQ-CT total score. **Secondary Endpoints:** • Percentage change from baseline to the end of the 3-month Core Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 3-month Core Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 3-month Core Period in BW in overweight/obese patients with PWS. **Safety Endpoints:** • Incidence of adverse events (AEs); • Vital signs; • Height and BMI; • Physical examinations; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, anti-drug antibodies [ADA], and insulin-like growth factor-1 [IGF-1]). **Pharmacokinetic Endpoints:** The PK endpoints will be described in details in the SAP and will include as the data allow: C_{max}, T_{max}, AUC_{0-4}, and other PK parameters of livoletide **Additional Endpoints:** • Change from baseline in: – CgGIS-H and CGIS-H scores; – CgGIC-H and CGIC-H scores; – CGI-I score; – CGI-S score; – Fasting (for approximately 8 hours) and postprandial glucose and insulin measurement (profile); – Appetite-NRS score; – DBC2-P score;

Criteria for Evaluation Continued:	– PedsQL™ Parent-Proxy age-appropriate Reports score; – ZBI score; – EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Evaluation of the measurement properties and interpretation of clinically meaningful HQ-CT change in the study population using blinded study data and according to a psychometric analysis plan; • Responder definition using anchor-based methods supplemented with both cumulative distribution function (CDF) and probability density function (PDF) to derive the responder threshold for meaningful change; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods. **PHASE 2b EXTENSION PERIOD** **Efficacy Endpoints:** • Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in HQ-CT total score; • Percentage change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in BW in overweight/obese patients with PWS. **Safety Endpoints:** • Incidence of AEs; • Vital signs; • Height and BMI; • Physical examinations; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1). **Pharmacokinetic endpoints:** Plasma livoletide PK parameters will be derived using non-compartmental methods. Where possible, the following PK parameters will be determined. Additional parameters may also be calculated as appropriate. Maximum concentration (C_{max}); time of C_{max} (t_{max}); observed minimum concentration (C_{min}); time of C_{min} (t_{min}); average concentration during the dosing interval (C_{avg}); fluctuation index over the dosing interval (FI); area under the concentration-time curve during the dosing interval ($AUC_{(0\text{-}tau)}$); apparent terminal rate constant (λz); apparent terminal half-life ($t_{1/2}$); apparent total

Criteria for Evaluation Continued:	body clearance (CL/F); apparent volume of distribution (Vz/F); accumulation ratio for $AUC_{(0\text{-}tau)}$ ($RAUC_{(0\text{-}tau)}$); accumulation ratio for C_{max} (RC_{max}); and linearity index (LI) as appropriate. **Endpoints for Additional Assessments:** • Change from baseline in: – CgGIS-H and CGIS-H scores; – CgGIC-H and CGIC-H scores; – CGI-I score; – CGI-S score; – Fasting (for approximately 8 hours) glucose and insulin measurement; – DBC2-P score; – PedsQL™ Parent-Proxy age-appropriate Reports score; – ZBI score; – EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods. **Phase 3** **PHASE 3 CORE PERIOD** **Primary endpoint:** Change from baseline to the end of the 6-month Core Period for HQ-CT total score. **Secondary Endpoints:** • Percentage change from baseline to the end of the 6-month Core Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 6-month Core Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 6-month Core Period in BW in overweight/obese patients with PWS. **Safety Endpoints:** • Incidence of AEs; • Vital signs; • Height and BMI; • Physical examinations; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).

Criteria for Evaluation Continued:	**Additional Endpoints:** • Change from baseline in: – CgGIS-H and CGIS-H scores; – CgGIC-H and CGIC-H scores; – CGI-I score; – CGI-S score; – Fasting (for approximately 8 hours) and postprandial glucose and insulin measurement (profile); – Appetite-NRS score; – DBC2-P score; – PedsQL^{TM} Parent-Proxy age-appropriate Reports score; – ZBI score; – EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods. **PHASE 3 EXTENSION PERIOD** **Efficacy Endpoints:** • Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in HQ-CT total score; • Percentage change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in BW in overweight/obese patients with PWS. **Safety Endpoints:** • Incidence of AEs; • Vital signs; • Height and BMI; • Physical examinations; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).

Criteria for Evaluation Continued:	**Endpoints for Additional Assessments:** • Change from baseline in: – CgGIS-H and CGIS-H scores; – CgGIC-H and CGIC-H scores; – CGI-I score; – CGI-S score; – Fasting (for approximately 8 hours) glucose and insulin measurement; – DBC2-P score; – PedsQL™ Parent-Proxy age-appropriate Reports score; – ZBI score; – EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.
Data Analysis:	**Phase 2b** **PHASE 2b CORE PERIOD** **Efficacy:** The primary analysis for the primary efficacy endpoint will be done using a mixed model repeated measures analysis (MMRM) on the change-from-baseline HQ-CT total score within the first 3 months. As a supportive analysis, an analysis of covariance (ANCOVA) on the change-from-baseline HQ-CT total score at 3months will be performed. **Safety:** All safety data will be listed by treatment group, variable, visit, and time point (if applicable) for individual patients. Adverse events will be tabulated and summarized according to the Medical Dictionary for Regulatory Activities (MedDRA). Safety laboratory evaluations, 12-lead ECG parameters, vital signs, physical examinations, and the other safety assessments (e.g. BMI, lipid profiles, HbA1c, lean body mass, etc.) will be summarized descriptively. **PHASE 2b EXTENSION PERIOD** **Efficacy:** An MMRM approach will be used to compare the change from baseline to the end of the 9-month Extension Period and the change from the end of the 3-month Core Period to the end of the 9-month Extension Period in HQ-CT total score. Similar statistical approaches will be used for the analyses of the secondary endpoints and additional assessments. **Safety:** All safety data will be listed by treatment group, variable, visit, and time point (if applicable) for individual patients. Adverse events will be tabulated and summarized according to MedDRA. Safety laboratory evaluations, 12-lead ECG parameters, vital signs, physical examinations, and the other safety assessments (e.g. BMI, lipid profiles, HbA1c, lean body mass, etc.) will be summarized descriptively. **Phase 3** Data analysis will be comparable to Phase 2b. **PHASE 3 CORE PERIOD** **Efficacy:** The primary analysis for the primary efficacy endpoint will be done using a mixed model repeated measures analysis (MMRM) on the change-from-baseline HQ-CT total score within the first 3 months. As a supportive analysis, an ANCOVA on the change-from-baseline HQ-CT total score at 6 months will be performed. **Safety:** All safety data will be listed by treatment group, variable, visit, and time point (if applicable) for individual patients. Adverse events will be tabulated and summarized according

Data Analysis Continued:	to MedDRA. Safety laboratory evaluations, 12-lead ECG parameters, vital signs, physical examinations, and the other safety assessments (e.g. BMI, lipid profiles, HbA1c, lean body mass, etc.) will be summarized descriptively. **PHASE 3 EXTENSION PERIOD** **Efficacy:** An MMRM approach will be used to compare the change from baseline to the end of the 6-month Extension Period and the change from the end of the 6-month Core Period to the end of the 6-month Extension Period in HQ-CT total score. Similar statistical approaches will be used for the analyses of the secondary endpoints and additional assessments. **Safety:** All safety data will be listed by treatment group, variable, visit, and time point (if applicable) for individual patients. Adverse events will be tabulated and summarized according to MedDRA. Safety laboratory evaluations, 12-lead ECG parameters, vital signs, physical examinations, and the other safety assessments (e.g. BMI, lipid profiles, HbA1c, lean body mass, etc.) will be summarized descriptively.
Safety Endpoints for the DMC review:	Safety data review will be performed at a regular basis during the trials by an external Data Monitoring Committee (DMC) operating independently of the Sponsor. The DMC will make recommendations for the conduct of the study based on safety data.

1.2 Schedule of Activities

1.2.1 Schedule of Activities for Phase 2b Core Period

Study Stage	Phase 2b Core Period				
	Screening[1]	Double-blind Treatment Period			
Visit#	V1	Randomization[2] V2	V3	V4	End of Core Period/ /ET Discontinuation V5
Study Week(s)	**-4 to -1**	**1**	**5**	**9**	**13**
Treatment Duration (weeks/months)	**-**	**-**	**4/1**	**8/2**	**12/3**
Study Day(s)	**-28 to -1**	**1**	**29**	**57**	**85**
Visit Window (±X days)	**0**	**0**	**3**	**3**	**3**
Informed consent and assign a study specific patient number	X				
Demography	X				
Medical history[3]	X				
Disease history[4]	X				
Inclusion/exclusion criteria	X				
IQ test[5]	X				
Concomitant medications	X	X	X	X	X
Physical examination[6]	X (C)	X (C)	X (A)	X (A)	X (C)
Vital signs[7]	X	X	X	X	X
WC, BW, and BMI[8]	X	X	X	X	X
Height[9]	X	X	X	X	X
12-lead ECG[10]	X	X[10]			X
DXA (total body fat mass, lean body mass, bone mineral density)[11]		X			X

[1] The screening period is up to 4 weeks.
[2] The randomization visit will occur a minimum of 2 weeks after the screening visit.
[3] Complete medical history will be obtained at screening and any clinically significant changes from the screening visit will be reported as AEs.
[4] A confirmed genetic diagnosis of PWS. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If the PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria.
[5] Collect IQ scores and dates of completion if available in patient's medical record.
[6] "C" for complete physical examination, "A" for abbreviated physical examination. See Section 10.1.4 for assessments to be performed during a physical examination.
[7] Vital signs (respiration rate, pulse rate, and blood pressure) will be measured sitting after the patient has rested comfortably for 5 minutes. See Section 10.1.2.
[8] Before breakfast. See Section 9.1.3 and Section 9.1.4.
[9] Before breakfast. See Section 10.1.3.
[10] See Section 10.1.6.
[11] DXA can be obtained within 2 weeks prior to randomization (Visit 2) and the End of Core Period visit (Visit 5). See Section 9.1.2 and Section 10.1.5.

Study Stage	Phase 2b Core Period				
	Screening[1]	Double-blind Treatment Period			
Visit#	V1	Randomization[2] V2	V3	V4	End of Core Period/ /ET Discontinuation V5
Study Week(s)	**-4 to -1**	**1**	**5**	**9**	**13**
Treatment Duration (weeks/months)	**-**	**-**	**4/1**	**8/2**	**12/3**
Study Day(s)	**-28 to -1**	**1**	**29**	**57**	**85**
Visit Window (±X days)	**0**	**0**	**3**	**3**	**3**
Pregnancy test[12]	X	X	X	X	X
Safety laboratory evaluations in the fasting condition[13]	X	X	X		X
Blood samples for PK analysis[14]			X		
Blood samples for HbA1c	X	X			X
Blood samples for glucose and insulin profiles[15]		X	X		X
Blood samples for AG and UAG profiles[15]		X	X		X
Blood samples for IGF-1		X			X
Blood samples for ADA analysis		X	X		X
Review and completion of questionnaires on eDevice [16]	X	X	X	X	X
Isocaloric breakfast taken on site and report any food not consumed[17]		X	X		X
Appetite-NRS[17]	X	X	X		X
HQ-CT	X	X	X	X	X
Quality of Life: PedsQL™ Parent-Proxy Report		X			X
CgGIS-H		X	X	X	X
CGIS-H		X	X	X	X
CgGIC-H			X	X	X
CGIC-H			X	X	X
CGI-I			X	X	X
CGI-S		X	X	X	X
Caregiver Disease Burden: ZBI		X			X
EQ-5D-5L Self-complete version and Proxy version 1		X			X
DBC2-P		X			X

[12] Pregnancy tests will be performed for women of childbearing potential only. See Section 8.1.2.2.3.

[13] Blood samples will be collected after fasting for approximately 8 hours. Clinical serum chemistries, hematology, coagulation, and urinalysis parameters are described in Section 8.1.2. Clinical laboratory evaluations will be performed centrally.

[14] PK samples (3-timepoint sampling) will be collected at the same time as glucose/insulin/AG/UAG profiles as outlined in the Pharmacokinetic Schedule of Activities provided in Section 1.2.3.

[15] Blood samples for glucose, insulin, AG, and UAG profiles will be collected after fasting for approximately 8 hours (all patients) and 30 minutes and 180 minutes post-start of an isocaloric breakfast (only patients 8 to 65 years of age).

[16] The eDevice will be used to collect data from all questionnaires and the appetite-NRS. Data from the questionnaires and appetite-NRS will be completed on the eDevice while on site, either by the caregiver, the patient (for the NRS), or by the investigator. The eDevice will not be dispensed to the patients.

[17] Appetite-NRS should be administered (only to patients 8 to 65 years of age) before (after fasting for approximately 8 hours), at the end, and 120 minutes post-start of an isocaloric breakfast, except at the screening visit, where NRS will be administered for training and acclimation purposes (no profile). Food not consumed when administered the isocaloric breakfast needs to be recorded. On-site consumption of isocaloric breakfast is not required for patients 4 to 7 years old.

Study Stage	**Phase 2b Core Period**				
	Screening[1]	**Double-blind Treatment Period**			
Visit#	**V1**	**Randomization**[2] **V2**	**V3**	**V4**	**End of Core Period/ /ET Discontinuation V5**
Study Week(s)	**-4 to -1**	**1**	**5**	**9**	**13**
Treatment Duration (weeks/months)	**-**	**-**	**4/1**	**8/2**	**12/3**
Study Day(s)	**-28 to -1**	**1**	**29**	**57**	**85**
Visit Window (±X days)	**0**	**0**	**3**	**3**	**3**
Review/record AEs	X----------				----------X
Randomization via IRT[18]		X			
Dispensation of glucometer kit[19]		X			
Dispensation of study drug		X	X	X	X
Drug accountability			X	X	X
On-site study drug administration (during treatment period only)		X	X	X	X

Abbreviations: ADA=anti-drug antibodies; AEs=adverse events; AG=acylated ghrelin; BMI=body mass index; BW=body weight; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; DXA= dual energy X-ray absorptiometry; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eDevice=electronic device; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; ET=Early Treatment; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; IGF-1=insulin-like growth factor-1; IQ=Intelligence Quotient; IRT=Interactive Response Technology; NRS=Numerical Rating Scale; PedsQL™=Pediatric Quality of Life inventory™; T2D=type 2 diabetes mellitus; UAG=unacylated ghrelin; V=visit; WC=waist circumference; ZBI= Zarit Burden Interview.

[18] Randomization via IRT should be performed on the first day of the double-blind treatment period.
[19] Glucometer will be provided to patients with T2D if necessary (i.e. if they do not have one).

1.2.2 Schedule of Activities for Phase 2b Extension Period

Study Stage	**Phase 2b Extension Period**				**End of Study**
Visit #	**V6**	**V7**	**V8**	**End of Extension Period/ Early Treatment Discontinuation V9**	**Telephone Follow-up V10**
Study Week(s)	**18**	**27**	**40**	**53**	**57**
Treatment Duration (weeks/months)	**17/4**	**26/6**	**39/9**	**52/12**	**-**
Study Day(s)	**120**	**183**	**274**	**365**	**393**
Visit Window (±X days)	**4**	**7**	**7**	**7**	7
Concomitant medications	X	X	X	X	X
Physical Examination[1]	X (C)	X (C)	X (A)	X (C)	
Vital Signs[2]	X	X	X	X	
WC, BW, and BMI[3]	X	X	X	X	
Height[4]	X	X	X	X	
12-lead ECG[5]		X[6]		X	
DXA (total body fat mass, lean body mass, bone mineral density)[6]		X		X	
Pregnancy test[7]	X	X	X	X	
Safety laboratory evaluations in the fasting condition[8]	X	X	X	X	
Blood samples for HbA1c		X	X	X	
Blood samples for fasting glucose and insulin[9]		X	X	X	
Blood samples for fasting AG and UAG analyses[9]		X		X	
Blood sample for IGF-1		X		X	
Blood sample for ADA analysis		X		X	

[1] "C" for complete physical examination, "A" for abbreviated physical examination. See Section 10.1.4 for assessments to be performed during a physical examination.
[2] Vital signs (respiration rate, pulse rate, and blood pressure) will be measured sitting after the patient has rested comfortably for 5 minutes. See Section 10.1.2.
[3] Before breakfast. See Section 9.1.3 and Section 9.1.4.
[4] Before breakfast. See Section 10.1.3.
[5] See Section 10.1.6.
[6] DXA can be obtained within 2 weeks prior to visit 7 and the End of Extension Period visit (Visit 9). See Section 9.1.2 and Section 10.1.5
[7] Pregnancy tests will be performed for women of childbearing potential only. See Section 8.1.2.2.3.
[8] Blood samples will be collected after fasting for approximately 8 hours. Clinical serum chemistries, hematology, coagulation, and urinalysis parameters are described in Section 8.1.2. Clinical laboratory evaluations will be performed centrally.
[9] Blood samples will be collected after fasting for approximately 8 hours.

Study Stage	**Phase 2b Extension Period**				**End of Study**
Visit #	**V6**	**V7**	**V8**	**End of Extension Period/ Early Treatment Discontinuation V9**	**Telephone Follow-up V10**
Study Week(s)	**18**	**27**	**40**	**53**	**57**
Treatment Duration (weeks/months)	**17/4**	**26/6**	**39/9**	**52/12**	**-**
Study Day(s)	**120**	**183**	**274**	**365**	**393**
Visit Window (±X days)	**4**	**7**	**7**	**7**	7
Blood samples for PK analysis[10]	X	X			
Review and completion of questionnaires on eDevice	X	X	X	X	
HQ-CT	X	X	X	X	
Quality of Life: PedsQL™ Parent-Proxy Report		X		X	
CgGIS-H	X	X	X	X	
CGIS-H	X	X	X	X	
CgGIC-H	X	X	X	X	
CGIC-H	X	X	X	X	
CGI-I	X	X	X	X	
CGI-S	X	X	X	X	
Caregiver Disease Burden: ZBI		X		X	
EQ-5D-5L Self-complete version and Proxy version 1		X		X	
DBC2-P		X		X	
Review/record AEs	X----------X				
Dispensation of study drug (livoletide)	X	X	X		
Drug accountability	X	X	X	X	
On-site livoletide administration	X	X	X	X	

Abbreviations: ADA=anti-drug antibodies; AEs=adverse events; AG=acylated ghrelin; BMI=body mass index; BW=body weight; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; DXA= dual energy X-ray absorptiometry; ECG=electrocardiogram; eDevice=electronic device; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; IGF-1=insulin-like growth factor-1; PedsQL™=Pediatric Quality of Life inventory™; PK=pharmacokinetic; UAG=unacylated ghrelin; V=visit; WC=waist circumference; ZBI= Zarit Burden Interview.

[10] PK samples (profile or sparse sampling) will be collected as outlined in the Pharmacokinetic Schedule of Activities provided in Section 1.2.3.

1.2.3 Pharmacokinetic Schedule of Activities

Pharmacokinetic sampling –	
Visit 3 (Week 5/Day 29)	*3-timepoint Sampling (all patients)* Blood samples should be drawn at the same time as glucose/insulin/AG/UAG profiles Pre-dose 30 min post start of breakfast 180 min post start of breakfast
Visit 6 (Week 18/Day 120)	*Profile Sampling (up to 20 patients per dose group)* Pre-dose 0.5 (± 2 min), 1 (± 5 min), 2 (± 5 min), 4 (± 5 min), 7 (± 60 min) hours post-dose
	Sparse Sampling (all patients not included in profile sampling) Pre-dose 1.5 hours (± 30 min) post-dose 3.5 hours (± 30 min) post-dose
Visit 7 (Week 27/Day 183)	*Sparse Sampling (all patients)* Pre-dose 1.5 hours (± 30 min) post-dose 3.5 hours (± 30 min) post-dose

Abbreviations: min=minutes.

1.2.4 Schedule of Activities for Phase 3 Core Period

Study Stage	**Phase 3 Core Period**						
	Screening[1]	**Double-blind Treatment Period**					
Visit#	**V1**	**Randomization**[2] **V2**	**V3**	**V4**	**V5**	**V6**	**End of Core Period /ET Discontinuation V7**
Study Week(s)	**-4 to -1**	**1**	**5**	**9**	**13**	**18**	**27**
Treatment Duration (weeks/months)	**-**	**-**	**4/1**	**8/2**	**12/3**	**17/4**	**26/6**
Study Day(s)	**-28 to -1**	**1**	**29**	**57**	**85**	**120**	**183**
Visit Window (±X days)	**0**	**0**	**3**	**3**	**3**	**3**	**3**
Informed Consent and assign a study specific patient number	X						
Demography	X						
Medical History[3]	X						
Disease History[4]	X						
Inclusion/Exclusion criteria	X						
IQ test[5]	X						
Concomitant medications	X	X	X	X	X	X	X
Physical Examination[6]	X (C)	X (C)	X (C)	X (A)	X (C)	X (A)	X (C)
Vital Signs[7]	X	X	X	X	X	X	X
WC, BW, and BMI[8]	X	X	X	X	X	X	X
Height[9]	X	X	X	X	X	X	X
12-lead ECG[10]	X	X					X
DXA (total body fat mass, lean body mass, bone mineral density)[11]		X			X		X
Pregnancy test[12]	X	X	X	X	X	X	X
Safety laboratory evaluations in the fasting condition [13]	X	X	X	X	X	X	X
Blood samples for HbA1c	X	X			X		X
Blood samples for glucose and insulin profile[14]		X	X		X		X

[1] The screening period is up to 4 weeks.
[2] The randomization visit will occur a minimum of 2 weeks after the screening visit.
[3] Complete medical history will be obtained at screening and any clinically significant changes from the screening visit will be reported as AEs.
[4] Diagnosis of PWS confirmed by DNA testing. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If the PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria.
[5] Collect IQ scores and dates of completion if available in patient's medical record.
[6] "C" for complete physical examination, "A" for abbreviated physical examination. See Section 10.1.4 for assessments to be performed during a physical examination.
[7] Vital signs (respiration rate, pulse rate, and blood pressure) will be measured sitting after the patient has rested comfortably for 5 minutes. See Section 10.1.2.
[8] Before breakfast. See Section 9.1.3 and Section 9.1.4.
[9] Before breakfast. See Section 10.1.3.
[10] See Section 10.1.6.
[11] DXA can be obtained within 2 weeks prior to the randomization (Visit 2), to Visit 5 and to End of Core Period visit (Visit 7). See Section 9.1.2 and Section 10.1.5.
[12] Pregnancy tests will be performed for women of childbearing potential only. See Section 8.1.2.2.3.
[13] Blood samples will be collected after fasting for approximately 8 hours. Clinical serum chemistries, hematology, coagulation, urinalysis parameters are described in Section 8.1.2. Clinical laboratory evaluations will be performed centrally.

Study Stage	**Phase 3 Core Period**						
	Screening[1]	**Double-blind Treatment Period**					
Visit#	**V1**	**Randomization**[2] **V2**	**V3**	**V4**	**V5**	**V6**	**End of Core Period /ET Discontinuation V7**
Study Week(s)	**-4 to -1**	**1**	**5**	**9**	**13**	**18**	**27**
Treatment Duration (weeks/months)	**-**	**-**	**4/1**	**8/2**	**12/3**	**17/4**	**26/6**
Study Day(s)	**-28 to -1**	**1**	**29**	**57**	**85**	**120**	**183**
Visit Window (±X days)	**0**	**0**	**3**	**3**	**3**	**3**	**3**
Blood samples for AG and UAG profile[14]		X	X		X		X
Blood samples for IGF-1		X			X		X
Blood samples for ADA analysis		X			X		X
Isocaloric breakfast on site and report any food not consumed		X	X		X		X
Review and completion of questionnaires on eDevice[15]	X	X	X	X	X	X	X
Appetite-NRS[16]	X	X	X		X		X
HQ-CT	X	X	X	X	X	X	X
Quality of Life: PedsQL™ Parent-Proxy Report		X			X		X
CgGIS-H		X	X	X	X	X	X
CGIS-H		X	X	X	X	X	X
CgGIC-H			X	X	X	X	X
CGIC-H			X	X	X	X	X
CGI-I			X	X	X	X	X
CGI-S		X	X	X	X	X	X
Caregiver Disease Burden: ZBI		X			X		X
EQ-5D-5L Self-complete version and Proxy version 1		X			X		X
DBC2-P		X			X		X
Review/record AEs	X---------- ----------X						
Randomization via IRT[17]		X					
Dispensation of glucometer kit[18]		X					
Dispensation of study drug		X	X	X	X	X	X
Drug accountability			X	X	X	X	X
On-site placebo or livoletide administration		X	X	X	X	X	X

[14] Blood samples for glucose, insulin, AG, and UAG profiles will be collected after fasting for approximately 8 hours and 30 minutes and 180 minutes post-start of an isocaloric breakfast.

[15] The eDevice will be used to collect data from all questionnaires and the appetite-NRS. Data from the questionnaires and appetite-NRS will be completed on the eDevice while on site, either by the caregiver, the patient (for the NRS), or by the investigator. The eDevice will not be dispensed to the patients.

[16] Appetite-NRS should be administered to patients before (after fasting for approximately 8 hours), at the end, and 120 minutes post-start of an isocaloric breakfast, except at the screening visit where NRS will be administered for training and acclimation purposes (no profile). Food not consumed when administered the isocaloric breakfast needs to be recorded.

[17] Randomization via IRT should be performed on the first day of the double-blind treatment period.

[18] Glucometer will be provided to patients with T2D if necessary (i.e. if they do not have one).

Abbreviations: ADA=anti-drug antibodies; AEs=adverse events; AG=acylated ghrelin; BMI=body mass index; BW=body weight; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; DXA= dual energy X-ray absorptiometry; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eDevice=electronic device; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; ET=Early Treatment; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; IGF-1=insulin-like growth factor-1; IQ=Intelligence Quotient; IRT=Interactive Response Technology; NRS=Numerical Rating Scale; PedsQL™=Pediatric Quality of Life inventory™; T2D=type 2 diabetes mellitus; UAG=unacylated ghrelin; V=visit; WC=waist circumference; ZBI=Zarit Burden Interview.

1.2.5 Schedule of Activities for Phase 3 Extension Period

Study Stage	**Phase 3 Extension Period**			**End of Study**
			End of Extension Period/ Early Treatment Discontinuation	**Telephone follow-up**
Visit#	**V8**	**V9**	**V10**	**V11**
Study Week(s)	**31**	**40**	**53**	**57**
Treatment Duration (weeks/months)	**30/7**	**39/9**	**52/12**	**-**
Study Day(s)	**211**	**274**	**365**	**393**
Visit Window (±X days)	**7**	**7**	**7**	7
Concomitant medications	X	X	X	X
Physical examination[1]	X (A)	X (C)	X (C)	
Vital signs[2]	X	X	X	
WC, BW, and BMI[3]	X	X	X	
Height[4]	X	X	X	
12-lead ECG[5]		X	X	
DXA (total body fat mass, lean body mass, bone mineral density)[6]		X	X	
Pregnancy test[7]	X	X	X	
Safety laboratory evaluations in the fasting condition[8]	X		X	
Blood samples for HbA1c		X	X	
Blood samples for fasting glucose and insulin[9]			X	
Blood samples for fasting AG and UAG analyses[10]			X	
Blood sample for IGF-1			X	
Blood sample for ADA analysis			X	
Review and completion of questionnaires on eDevice	X	X	X	
HQ-CT	X	X	X	
Quality of Life: PedsQL™ Parent-Proxy Report			X	
CgGIS-H	X	X	X	
CGIS-H	X	X	X	
CgGIC-H	X	X	X	
CGIC-H	X	X	X	
CGI-I	X	X	X	

[1] "C" for complete physical examination, "A" for abbreviated physical examination. See Section 10.1.4 for assessments to be performed during a physical examination.
[2] Vital signs (respiration rate, pulse rate, and blood pressure) will be measured sitting after the patient has rested comfortably for 5 minutes. See Section 10.1.2.
[3] Before breakfast. See Section 9.1.3 and Section 9.1.4.
[4] Before breakfast. See Section 10.1.3.
[5] See Section 10.1.6.
[6] DXA can be obtained with 2 weeks prior to Visit 9 and End of Extension Period visit (Visit 10). See Section 9.1.2 and Section 10.1.5.
[7] Pregnancy tests will be performed women of childbearing potential only. See Section 8.1.2.2.3.
[8] Blood samples will be collected after fasting for approximately 8 hours. Clinical serum chemistries, hematology, coagulation, urinalysis parameters are described in Section 8.1.2. Clinical laboratory evaluations will be performed centrally.
[9] Blood samples will be collected after fasting for approximately 8 hours.

Study Stage	**Phase 3 Extension Period**			**End of Study**
Visit#	**V8**	**V9**	**End of Extension Period/ Early Treatment Discontinuation V10**	**Telephone follow-up V11**
Study Week(s)	**31**	**40**	**53**	**57**
Treatment Duration (weeks/months)	**30/7**	**39/9**	**52/12**	**-**
Study Day(s)	**211**	**274**	**365**	**393**
Visit Window (±X days)	**7**	**7**	**7**	7
CGI-S	X	X	X	
Caregiver Disease Burden: ZBI			X	
EQ-5D-5L Self-complete version and Proxy version 1			X	
DBC2-P			X	
Review/record AEs	X----------X			
Dispensation of livoletide	X	X		
Drug accountability	X	X	X	
On-site livoletide administration	X	X	X	

Abbreviations: ADA=anti-drug antibodies; AEs=adverse events; AG=acylated ghrelin; BMI=body mass index; BW=body weight; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; DXA= dual energy X-ray absorptiometry; ECG=electrocardiogram; eDevice=electronic device; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; IGF-1=insulin-like growth factor-1; NRS=Numerical Rating Scale; PedsQL™=Pediatric Quality of Life inventory™; UAG=unacylated ghrelin; V=visit; WC=waist circumference; ZBI= Zarit Burden Interview.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

AZP-531 is an 8-amino acid, cyclic, peptide analog of unacylated ghrelin (UAG). This study will evaluate AZP-531 for the treatment of hyperphagia and food-related behaviors in patients with Prader-Willi syndrome (PWS). All relevant information concerning the compound is available in the latest version of the Investigator's Brochure (IB).

2.1 Background Information

2.1.1 Overview of Prader-Willi Syndrome

Prader-Willi syndrome is a rare disease (in Europe, the prevalence ranges between 1 and 9 per 100,000 – source Orphanet, last consultation March 06, 2018). It is a neurodevelopmental and hypothalamic disorder, equally affecting both sexes, due to genetic abnormalities that result in the absence of expression of genes at the locus q11-q13 on chromosome 15 (1). Approximately 60-65% of affected individuals have a deletion of the paternal chromosome 15q11-q13 while most of the remaining patients display a maternal uniparental disomy for chromosome 15. A small percentage of patients may have abnormalities of the imprinting center or translocation involving chromosome 15.

Prader-Willi syndrome is associated with dysmorphic features, short stature, growth hormone deficiency, hypogonadism, low calorie expenditure, and abnormal body composition with reduced fat free mass and increased fat mass. Cognitive impairments, behavioral disturbances, as well as psychiatric disorders are also part of the syndrome (2).

The growing understanding of the natural history of PWS has recently led to the identification of several successive nutritional and eating behavior phases proceeding from poor feeding, through normal eating without and with obesity, to hyperphagia and life-threatening obesity (3).

2.1.2 Hyperphagia Associated with Prader-Willi Syndrome

Hyperphagia is a significant, salient, and constant feature of the syndrome and is associated with abnormal and extreme behaviors towards food including obsessive food seeking, food storage, foraging, and hoarding (see Figure 1); all of these representing a lifelong source of distress and severely and negatively affecting social adaptation, occupational performance, and quality of life (QoL) (4, 5). Hyperphagia and abnormal food-related behaviors may result in life-threatening complications such as choking or gastric necrosis and rupture (6-8). This condition is associated with significant morbidity resulting from obesity, type 2 diabetes (T2D), and related complications that altogether contribute to reduced life expectancy (8-10).

In addition to the direct impact that hyperphagia has on individuals suffering from PWS, the health-related quality of life (HRQoL) both for individuals and for their caregivers (5) and their families (11) is also affected.

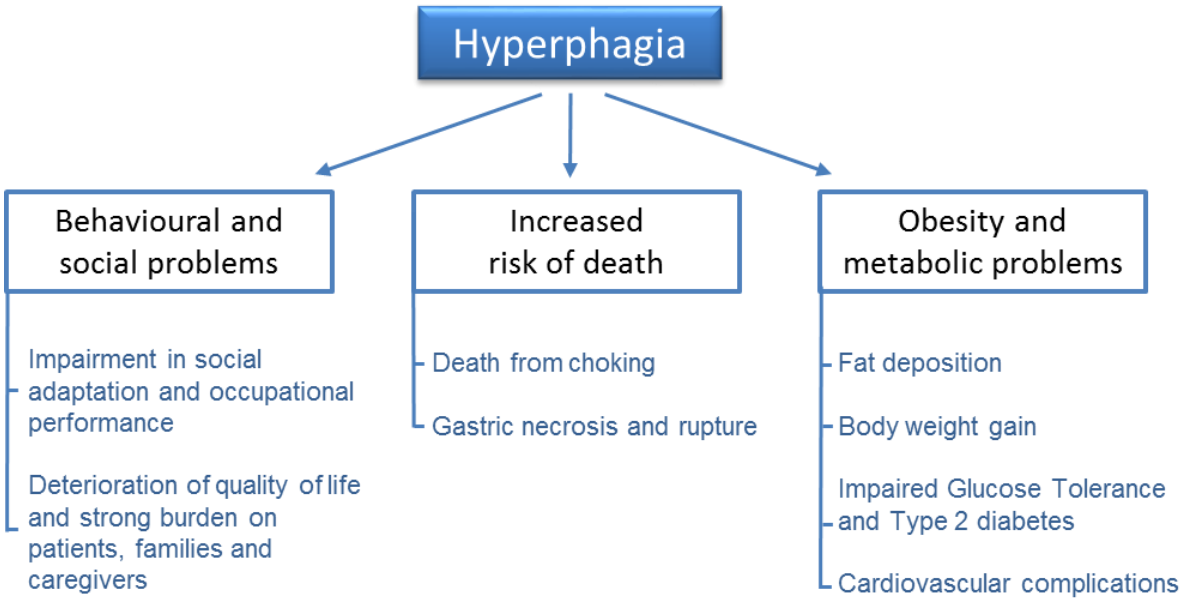


Figure 1: Complications associated with hyperphagia in patients with Prader-Willi syndrome

2.1.3 Current Therapeutic Options for Hyperphagia associated with Prader-Willi Syndrome

Currently, there are no effective pharmacological treatment options for hyperphagia and excessive eating behaviors associated with PWS. Management of food-related behaviors and obesity is problematic and represents one of the highest priority medical needs in PWS. Data from a recent survey performed by the United States (US) and Canadian Foundation for Prader-Willi Research in 779 parents revealed that 74% of them would look at reduction of hunger as most important for an ideal treatment for PWS (12).

To date, continuous lifelong supervision, strict control over access to food, dietary restriction, and regular exercise are still the only available options. Growth hormone, which has been used since the early 2000's for improvement in growth velocity and body composition, does not ameliorate PWS-associated hyperphagia (13, 14). Similarly, anorexigenic agents, endocannabinoid antagonists, and gastric banding or bypass, have been proven ineffective in reducing hyperphagia or were associated with safety issues (15-17).

Over the past few years, PWS's orphan indication and the significant unmet medical need has led a number of pharmaceutical companies to initiate clinical investigation programs in PWS; however, to date there are no therapies approved for the treatment of hyperphagia in PWS.

2.1.4 Introduction to Ghrelin Biology

Ghrelin is a 28-amino acid peptide hormone produced predominantly by the stomach and expressed in lower amounts in a variety of organs including the gastrointestinal tract, pancreas, brain, pituitary gland, kidney, lung, and heart (18).

In the circulation, ghrelin is present in 2 forms (19): 1) the acylated ghrelin (AG) that has orexigenic, obesogenic, and diabetogenic properties (20-28) and 2) the UAG, also known as des-acyl ghrelin, that has been shown to inhibit AG effects (29-36).

Unacylated ghrelin is acylated by ghrelin O-acyltransferase (GOAT) on the serine-3 residue (37) to yield AG as shown in Figure 2 below:

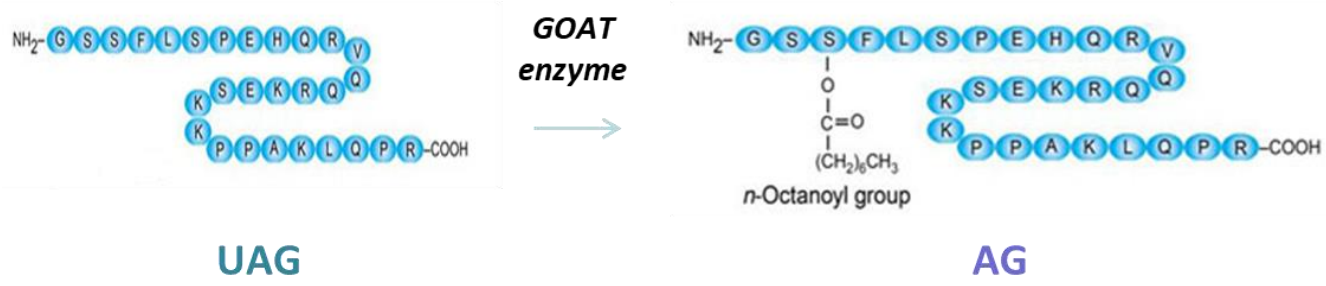


Figure 2: Unacylated ghrelin (UAG) acylation by ghrelin O-acyltransferase (GOAT)

Acylated Ghrelin

Acylated ghrelin, commonly referred to as ghrelin, is a pleiotropic hormone, discovered for its property to activate the growth hormone secretagogue receptor (GHSR) (18) that contributes to the regulation of key endocrine and non-endocrine functions including glucose and lipid metabolism. Acylated ghrelin is one of the most powerful orexigenic agents and the only one acting in the periphery in animals and humans (20-23). The effect on appetite is mainly achieved through GHSR of hypothalamic neurons co-expressing Neuropeptide Y and agouti-related protein (AgRP) (25). Plasma AG levels peak before meals, normalize after feeding, and appear to be regulated by the nutritional status (24). In addition to induction of food intake, administration of AG is adipogenic, hyperglycemic, and induces insulin resistance (26-28).

Unacylated Ghrelin

Unacylated ghrelin is devoid of the acyl moiety and is unable to bind the GHSR at physiological concentrations (18, 38). Because it does not bind to GHSR, UAG was first considered as a degradation product with no biological activities. Data accumulated over the years has provided insights that UAG counteracts the metabolic effects of AG and the effects of AG on food consumption. In animals, administration of UAG improved glucose intolerance, inhibited fat mass deposition, and reduced body weight (BW) gain (39-42). UAG overexpression in transgenic mice also resulted in improvement of glucose tolerance and insulin sensitivity as well as reduced fat mass and resistance to high fat diet-induced obesity (43, 44). In humans, co-administration of AG and UAG counteracted the increase in glucose and decrease in insulin, while administration of UAG alone had no effect (29). In addition, UAG has intrinsic direct activities for protection of various tissues including beta islets, muscle, vessels, heart, and brain (45-50).

In animal models, where increased food intake is induced by exogenous administration of AG, administration of UAG has been shown to counteract this effect (31, 35, 36). In the rodent models, data suggest that UAG inhibits AG-induced hypothalamic neuronal activity through AG-independent neuronal pathways, possibly involving nesfatin-1 immunopositive neurons (31)

and/or melanocortin receptors (increased melanocortin-4 receptor [MC4R] and decreased melanocortin-3 receptor [MC3R]) in the hypothalamus (35).

Acylated Ghrelin and Unacylated Acylated Ghrelin Levels in Prader-Willi Syndrome

Although the basis for the excessive eating behavior observed in PWS is not yet completely understood, evidence supports involvement of appetite hormone disturbances and dysregulation of the hypothalamus area controlling appetite.

Several studies have consistently documented increased fasting and postprandial circulating levels of total ghrelin in patients with PWS at all ages, as compared to control lean and obese subjects (51-54). In addition, in adults with PWS, plasma total ghrelin levels were also shown to positively correlate with ratings of hunger, which suggests that ghrelin may be responsible, at least in part, for the hyperphagia observed in PWS (54).

In an observational study that included 138 children and adults with PWS, Kuppens and colleagues (55) showed that AG levels were globally elevated in patients with PWS as compared to those of healthy controls and obese subjects, while UAG levels were similar (Figure 3A).

When looking specifically at AG and UAG levels according to the PWS nutritional phases (Figure 3B), UAG levels were showed to be significantly higher than AG levels in early nutritional phases. This is also documented by a recent study from Beauloye and colleagues that was conducted in infants with PWS (37 control and 100 infants with PWS from 1 month to 4 years of age) (56). In the Kuppens study, the onset of hyperphagia and obesity (Phase 2a) is associated with a drastic drop in UAG levels, yet no change in AG levels. As a result, the AU/UAG ratio increased with progression of nutritional phases and severity of hyperphagia. It is hypothesized that this considerable change in the AG/UAG ratio drives the switch to hyperphagia and obesity. Altogether, these results indicate that PWS hyperphagia is associated with high levels of orexigenic AG and a relative UAG deficiency.

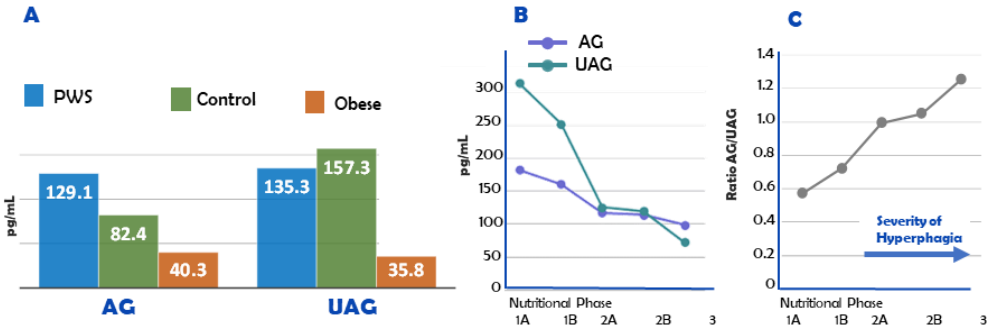


Figure 3: AG and UAG levels in PWS, control, and obese subjects (A) and evolution of AG and UAG levels in nutritional phases in PWS (B). Adapted from Kuppens et al., 2015

Abbreviations: AG=acylated ghrelin; PWS=Prader-Willi syndrome; UAG=unacylated ghrelin.

2.2 The Investigational Drug: Livoletide, an Unacylated Ghrelin Analog

2.2.1 Livoletide: General Description

Since its discovery, the ghrelin system has emerged as a pharmacological target for the treatment of a broad variety of diseases. In particular, various pharmacological tools including GHSR antagonists, AG-blocking agents, and GOAT inhibitors, have been designed with the objective of antagonizing or blocking the effects of AG on food intake, fat mass, and/or glucose. None of the designed GHSR antagonist and AG-blocking drug candidates has moved to clinical testing, to our knowledge, because of lack of efficacy and unwanted effects observed in animal models (37). Unacylated ghrelin pharmacological profile that includes both direct protective effects on tissues and a unique potency to functionally counteract AG metabolic activities and AG effect on food intake has provided the rationale for opening a new therapeutic class for the treatment of metabolic diseases and specifically PWS.

However, UAG itself is subject to rapid proteolytic cleavage resulting in short duration of action. Thus, for pharmaceutical development purposes, a series of UAG analogs were designed. Analog UAG 6-13 (AZP-502), that does not contain serine 3, was found to be the smallest and most effective fragment able to mimic effect of full length UAG and was shown, as UAG, to prevent diabetes in streptozotocin-treated rats (57).

Cyclization of the UAG 6-13 fragment improved *in vitro* plasma stability and *in vivo* half-life in animals and humans and resulted in livoletide (also known as AZP-531), a peptide analog of 8 amino acids suitable for daily subcutaneous (SC) injection (58, 59). Livoletide has shown a comparable pharmacological profile to UAG and AZP-502, its linear counterpart, in both *in vitro* and *in vivo* models (40, 50, 57), including a rat model where livoletide counteracts AG-induced food intake. On the basis of this pharmacological profile, livoletide has been selected as a drug candidate for clinical development. The structures of UAG, AZP-502, and livoletide are presented below (Figure 4).

Figure 4: Structure of unacylated ghrelin (UAG), AZP-502, and livoletide (AZP-531)

2.2.2 Chemistry and Description

Livoletide is the acetate salt of cyclo human UAG (6-13). The chemical name is Glutamyl-Histidyl-Glutaminyl-Arginyl-Valyl-Glutaminyl-Seryl-Propyl, Cyclic 1-8, acetate counter ion, abbreviated as follows:

Glu-His-Gln-Arg-Val-Gln-Ser-Pro

The structural formula of livoletide is presented in Figure 5 below.

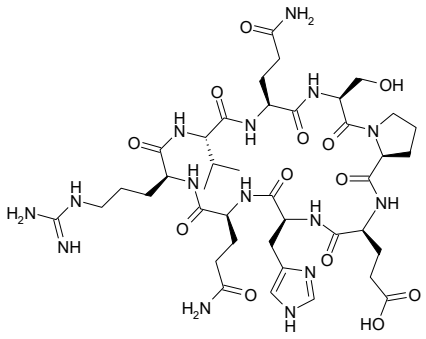


Figure 5: Structural formula of livoletide (AZP-531)

The peptide is synthesized using N-(Fluorenyl-9-MethOxyCarbonyl) chemistry on solid phase in compliance with Good Manufacturing Practice (GMP).

2.3 Summary of Relevant Nonclinical and Clinical Research

All nonclinical and clinical data that are relevant to the trial and that provide background for the trial are extensively described and available in the latest version of the IB. The following sections provide a summary of key significant nonclinical and clinical findings.

2.3.1 Nonclinical Studies

Efficacy Results

Proof-of-concept for the use of livoletide in PWS has been performed using a published rat model of inhibition of AG-induced food intake by UAG (31). In this model, livoletide was shown to significantly inhibit the effect of AG on cumulative food intake over a 2-hour feeding period.

Pharmacology

In vitro stability of livoletide was investigated in human plasma (58). Compared to AZP-502, the UAG 6-13 linear fragment, livoletide has increased stability. No degradation of livoletide was noted after 3 days of incubation at 37°C while its linear counterpart was degraded very quickly.

When administered subcutaneously or intravenously to animals, livoletide was measured for up to 4 hours (in rats) and 8 hours (in dogs). Subcutaneous bioavailability of livoletide was 96% and 85% in rats and dogs, respectively. Livoletide half-life was about 30 minutes in the rat and 1 hour in the dog.

Tissue distribution after SC administration of [^{3}H] radiolabeled livoletide was assessed in a whole-body autoradiography study in male and female rats. In both genders, distribution was rapid and widespread, with the highest concentration of total radioactivity observed in the kidney. Concentrations of radioactivity in the spinal cord and brain were low throughout the study period, indicating that drug-related radioactivity was not crossing the blood-brain barrier to any significant extent.

Safety

Core safety pharmacology studies with livoletide were performed in an Organization for Economic Co-operation and Development (OECD) member country in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP). No treatment related effects on major physiological systems including the cardiovascular system, respiratory system, and central nervous system were reported with livoletide.

Results of GLP repeat dose toxicology studies indicate that livoletide administered by SC injection for 14 days was associated with no systemic toxicity at doses up to 2 x 18 mg/kg/day and 2 x 5.5 mg/kg/day in rats and dogs, respectively.

Livoletide treatment caused minimal to moderate granulomatous SC inflammation associated with accumulation of foreign material, likely to be the test item, at some injection sites of a few treated animals (dogs) from all dose level groups. No anti-livoletide antibodies were noted at the end of the 14-day treatment period in either species.

Good Laboratory Practice chronic 13-week toxicology studies were conducted. Results showed no systemic toxicity at doses up to 75 mg/kg/day and 30 mg/kg/day in rats and dogs, respectively. These doses provide a group mean area under the concentration-time curve (AUC) value of equal or greater than 50-fold the intended clinical systemic exposure. In the dog study, minimal granulomatous inflammation comparable to what was observed in the 14-week study was noted at one injection site of one control and one low dose group (10 mg/kg/day). No anti-livoletide antibodies were noted at the end of the 13-week treatment period in either species.

Good Laboratory Practice chronic 26-week (rats) and 39-week (dogs) toxicology studies were conducted. Daily subcutaneous administration of livoletide at doses of 15, 30 and 45 mg/kg/day in the Wistar rat (for 26 consecutive weeks) or 3, 10 and 30 mg/kg/day in Beagle dogs (for 39 consecutive weeks) was not associated with any evidence of overt systemic toxicity. Consequently, the high doses tested (45 mg/kg/day and 30 mg/kg/day respectively) could be considered as the NOAELs. Corresponding mean toxicokinetic values for C_{max} and AUC0-24h (males/females) in rats were respectively 54.5/51.5 µg/mL and 129/112 µg.h/mL. Corresponding mean toxicokinetic values for C_{max} and AUC (males/females) in dogs were respectively 42.5/44.7 µg/mL and 119/113 µg.h/mL.

Good Laboratory Practice preliminary embryo-fetal and development studies in rats and rabbits have been completed and data show that livoletide doses up to 75 mg/kg/day (rat) and 120 mg/kg/day (rabbit) was not associated with embryo-fetal toxicity or teratogenic potential.

To support the inclusion of patients 4-to-7-year-old in the study, a Good Laboratory Practice rat juvenile study has been conducted. Livoletide given daily by subcutaneous administration at doses of 10, 25 and 75 mg/kg/day to the juvenile Wistar rat from the age of weaning (i.e., at 21 days of age) up to at least 12 weeks of age was well tolerated and was not associated with any evidence of overt systemic toxicity. In this study, toxicokinetic profiles were comparable to adult rats. This indicates comparable exposures for the same dose independent of age.

2.3.2 Clinical Experience with Livoletide

Table 1 below summarizes all completed clinical studies on livoletide to date.

PHASE STUDY NB *PUBLICATION*	PART	OBJECTIVES	STUDY DESIGN	TEST PRODUCT/ ROUTE	DURATION OF TREATMENT	STUDY POPULATION	NB SUBJECTS (AZP-531)
Phase 1 **AZP01-CLI-001** ***Allas et al., 2016*** [59]	Part A	Safety PK PD	Randomized placebo-controlled SAD	0.3, 3, 15, 30, 60, 120 µg/kg AZP-531 or placebo once a day/ SC	Single-dose	Male healthy subjects Age: 20-50 years BMI: 20.2-27.3 kg/m²	44 (33)
	Part B	Safety PK PD	Randomized placebo-controlled MAD	3, 15, 30, 60 µg/kg AZP-531 or placebo once a day/ SC	14 days	Overweight/obese subjects Age: 21-61 years BMI: 28- 37 kg/m²	32 (24)
	Part C	Safety PK PD	Randomized placebo-controlled MAD	15, 60 µg/kg AZP-531 once a day, 30 µg/kg AZP-531 BID or placebo/ SC	14 days	Subjects with T2D Age: 34-64 years BMI: 24-39 kg/m²	36 (27)
Phase 2a **AZP01-CLI-002** **Allas et al., 2017** [60]	Not applicable	Safety PD Efficacy	Randomized placebo-controlled	• 50-70 kg BW: 3 mg AZP-531 • 70 kg BW: 4 mg AZP-531 or placebo once a day/ SC	14 days	Adult and adolescent patients with PWS Age: 13-46 years BMI: 20.6-67.4 kg/m²	47 (23)

Table 1: Tabular summary of completed clinical studies on livoletide (AZP-531)

Abbreviations: AZP-531=livoletide; BID=twice daily; BMI=body mass index; BW=body weight; MAD=multiple ascending dose; NB=number; PD=pharmacodynamics; PK=pharmacokinetics; PWS=Prader-Willi syndrome; SAD=single ascending dose; SC=subcutaneous; T2D=type 2 diabetes.

Phase 1 Study (AZP01-CLI-001)

Livoletide has been tested in a 3-part, Phase 1, first-in-human, placebo-controlled study conducted in a single phase 1 unit (59). Part A was a single ascending dose (SAD) study conducted to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of livoletide in healthy male adult volunteers at the doses of 0.3, 3, 15, 30, 60, and 120 µg/kg. Part B was a multiple ascending dose (MAD) study conducted to evaluate tolerability, PK, and PD in male and female obese/overweight subjects following repeated daily administration of livoletide for 14 days at doses of 3, 15, 30, and 60 µg/kg. Part C was a MAD study conducted to evaluate tolerability, PK, and PD in male and female subjects with imperfectly controlled T2D following repeated daily administration of livoletide for 14 days at doses of 15, 2 x 30, and 60 µg/kg.

This study showed that livoletide was well tolerated at the doses tested. There were neither serious nor severe adverse events (AEs) in any part of the study. There were no significant

findings with respect to clinical laboratory safety tests, vital signs, electrocardiogram (ECG; performed in all parts), and telemetry (performed in SAD only).

Pharmacokinetics

Livoletide PK parameters were comparable overall at the same doses in the 3 study parts. In Part B and C, single and multiple-dose PK parameters were similar. Livoletide was rapidly absorbed reaching peak concentrations within approximately 1 hour. The half-life ranged between 2 and 3 hours. Maximum concentration (C_{max}) and AUC were dose-related and increased proportionally with the dose administered. Daily SC administration resulted in 24-hour exposure to livoletide at doses above 30 µg/kg. Accumulations in maximum and total exposures were negligible following repeated dosing for 14 days.

Pharmacodynamics

In Part B, PD findings included reductions in blood and interstitial glucose levels as well as reductions in BW after 14 days of administration of livoletide to subjects at doses ranging from 15 µg/kg to 60 µg/kg (-2.6 kg vs -0.8 kg for placebo). Insulin levels were unchanged, consistent with an insulin-sensitizing effect. In Part C, glucose parameters improved in all groups including placebo, suggesting a study effect in uncontrolled patients at baseline. Notwithstanding, livoletide at the dose of 60 µg/kg reduced glycated hemoglobin (HbA1c) by 0.4% (vs 0.2% for placebo) and BW by -2.1 kg (vs -1.4 kg for placebo).

Phase 2a Study (AZP01-CLI-002)

A randomized, double-blind, placebo-controlled Phase 2a clinical trial was conducted to assess the safety, tolerability, and preliminary efficacy on food-related behavior of daily SC administrations of livoletide to patients with PWS. The study was performed in 47 male and female patients with genetically confirmed PWS and evidence of increased appetite and hyperphagia. This study was carried out in 7 sites across France, Spain, and Italy. Doses of 3 to 4 mg of livoletide were administered SC daily for a total of 14 days.

In this study, livoletide was well tolerated with no serious or severe AEs and no clinically significant changes with respect to safety laboratory tests. Results show a significant improvement in caregiver-observed food-related behavior in patients treated with livoletide, as assessed by the Hyperphagia Questionnaire (HQ) (61), with a particular improvement in the Hyperphagic Severity domain score of the HQ. The highest improvement was observed in livoletide subjects with the highest hyperphagia score at baseline. These findings were supported by a reduction in patient-reported appetite following breakfast in patients treated with livoletide, as assessed by a patient-reported appetite-Numeric Rating Scale (NRS). Body weight did not change in both groups while a significant reduction in waist circumference (WC) and fat mass was observed only with livoletide. Livoletide significantly decreased postprandial glucose levels in a baseline glucose dependent fashion.

2.4 Rationale for Developing Livoletide in the Treatment of Hyperphagia in Patients with Prader-Willi Syndrome

The development of livoletide in the treatment of hyperphagia in patients with PWS was based on the following observations:

1. Plasma levels of AG are elevated in patients with PWS (with a relative deficit in UAG levels) and are hypothesized to contribute to the pathophysiology of hyperphagia.
2. In animal models, where increased food intake is induced by exogenous administration of AG, administration of livoletide (similar to UAG) has been shown to inhibit this effect.
3. Administration of livoletide to animals has been shown to prevent glucose intolerance, insulin resistance, and fat accumulation.

It has been hypothesized that administration of livoletide in patients with PWS improves hyperphagia and food related behaviors and provides additional metabolic benefits including inhibition of fat deposition and weight gain as well as improvement of insulin sensitivity.

Phase 1 data have indicated that livoletide administered for up to 14 days to obese subjects and patients with T2D at doses up to 60 μg/kg/day was well tolerated and resulted in improvement in metabolic parameters including BW and glucose control. Phase 2a results showed that a 14-day treatment with livoletide at doses up to 4 mg/day in patients with PWS was well tolerated and was associated with a significant improvement in food-related behaviors, as assessed by the HQ, supported by a reduction in patient-reported appetite, along with glucose control improvement, a reduction in WC, and a reduction in fat mass.

Altogether, these observations provide initial safety and efficacy of livoletide and support the conduct of larger and long term clinical trials in patients with PWS.

The single, pivotal Phase 2b/3 protocol provides greater efficiency than two separate studies as considerable site resources are required during study start-up and close-out activities. This is especially important in an orphan indication where the number of high quality investigator sites is limited. By combining the Phase 2b and Phase 3 studies into a single protocol, with nearly identical study design elements for both phases, sites may shift resource to protocol execution and patient care.

2.5 Potential Risks and Benefits to Human Participants

2.5.1 Known Potential Risks

Please refer to the IB for livoletide for an expanded risk/benefit assessment.

Animal Toxicology

Non-clinical repeated-dose toxicity studies in rats and dogs, which may be relevant to human safety, revealed the following:

- In dogs, livoletide treatment caused minimal to moderate granulomatous SC inflammation associated with accumulation of foreign material, likely to be the test item, at some injection sites of a few treated animals from all dose level groups (5 out of 18 animals);
- No anti-livoletide antibodies were noted at the end of the 14-day treatment period in either species.

Good Laboratory Practice chronic 13-week toxicology studies were conducted. Results show no systemic toxicity at doses up to 75 mg/kg/day and 30 mg/kg/day in rats and dogs, respectively.

These doses provide a group mean AUC value of greater than 50-fold the intended clinical systemic exposure. In the dog study, minimal granulomatous inflammation comparable to what was observed in the 14-week study was noted at one injection site of one control and one low dose group (10 mg/kg/day). No anti-livoletide antibodies were noted at the end of the 13-week treatment period in either species.

Good Laboratory Practice chronic 26-week (rats) and 39-week (dogs) toxicology studies were conducted and were not associated with any evidence of overt systemic toxicity. Good Laboratory Practice preliminary embryo-fetal and development studies in rats and rabbits have been completed and data show that livoletide doses up to 75 mg/kg/day (rat) and 120 mg/kg/day (rabbit) were not associated with embryo-fetal toxicity or of a teratogenic potential.

In addition, to support the inclusion of patients 4-to-7-year-old in the study, a Good Laboratory Practice rat juvenile study has been conducted. Livoletide given daily by subcutaneous administration at doses of 10, 25 and 75 mg/kg/day to the juvenile Wistar rat from the age of weaning (i.e., at 21 days of age) up to at least 12 weeks of age was well tolerated and was not associated with any evidence of overt systemic toxicity. In this study, toxicokinetic profiles were comparable to adult rats. This indicates comparable exposures for the same dose independent of age.

Anticipated Safety Profile

In a 3-part Phase I, randomized, placebo-controlled study (refer to Section 2.3.2 for details on study design), administration of livoletide was well tolerated, without serious or severe AEs.

In healthy volunteers (Part A), the most common treatment-emergent AE (TEAE) reported was injection site erythema in 4 subjects at 120 µg/kg livoletide (in one or both injection sites) and in 1 subject on placebo. In obese subjects (Part B), the most common TEAE reported was injection site reaction (4/24 subjects receiving livoletide and 1/8 subjects in the placebo group) followed by diarrhea (2/24 subjects receiving livoletide). In patients with T2D (Part C), the most common TEAE reported was diarrhea (5/27 subjects receiving livoletide and 1/9 receiving placebo), hematoma (4/24 subjects receiving livoletide), headache (2/9 subjects receiving placebo), and musculoskeletal pain (2/9 subjects receiving placebo).

No hypoglycemia event occurred in any study part. No clinically significant findings were noted with respect to hematology, coagulation, blood chemistry, urinalysis, or vital signs in any study part. Cardiac assessments (telemetry in Part A and ECG in Part B and C) revealed no significant findings at the end of the treatment period.

In patients with PWS (refer to Section 2.3.2 for details on study design), administration of livoletide for 14 days was well tolerated. There were transient injection site reactions which were seen at a higher frequency in the placebo group. There were no serious adverse events (SAEs) or AEs leading to study or treatment discontinuation, and no hypoglycemia events. There were no significant findings with respect to vital sign parameters and safety laboratory tests.

Systemic side-effects following long-term treatment that may occur in patients with PWS cannot be reliably predicted. As granulomatous inflammation was observed locally at the injection sites in the dog toxicology study and injection site reactions possibly related to livoletide were noted during the Phase I study, patients in this study will be monitored for injection site reactions.

Although pre-clinical and clinical studies with livoletide have not indicated or revealed any hypoglycemia event to date at the doses tested, a theoretical slight possibility of hypoglycemia still exists. In this study, blood glucose in patients with T2D will be monitored daily, fasting, during the study period using a glucometer.

No anti-livoletide antibodies were observed in both the rat and dog 3-month toxicology studies. In the Phase 1 and 2 clinical trials, samples for antibody analysis were collected but not analyzed as administration of livoletide was well tolerated with no significant drug reactions. In this study, samples for analysis of antibodies will be collected and analyzed.

Safety and efficacy of livoletide during pregnancy have not been established. Although fertility is extremely rare in PWS and only a few cases of pregnancy have been reported in the literature (62), all post-menarchal female patients who will be included in the study must have a negative pregnancy test at randomization. In addition, Women of Child Bearing Potential (WCBP), sexually active male patients, and all male partners of female patients should agree to use adequate methods of birth control throughout the study and for 30 days after the last dose of study drug.

2.5.2 Known Potential Benefits

Phase 2a results showed a significant improvement in caregiver-observed food-related behavior in patients treated with livoletide, as assessed by the HQ, which was supported by a reduction in patient-reported appetite following breakfast, as assessed by a patient-reported appetite-NRS. Over the 14-day treatment, BW did not change in both groups while a significant reduction in WC and fat mass was observed in patients treated with livoletide. Livoletide significantly decreased postprandial glucose levels in a baseline glucose dependent fashion

It is therefore hypothesized that significant improvement in food related behavior will be observed after a long-term treatment period with livoletide as well as the potential for improvement across multiple metabolic parameters including body composition and glycemic parameters.

2.5.3 Summary

Given the non-clinical safety profile of livoletide and available safety and initial efficacy data of livoletide in clinical studies conducted so far in healthy volunteers, obese subjects, patients with T2D, and patients with PWS, and in view of the unmet need in these patients, there is an appropriate potential benefit to risk consideration to study livoletide in hyperphagic patients with PWS.

3 OBJECTIVES AND ENDPOINTS

3.1 Tabular Summary of Trial Objectives and Endpoints

3.1.1 Phase 2b Tabular Summary of Trial Objectives and Endpoints

OBJECTIVES	ENDPOINTS
PHASE 2B CORE PERIOD	
Primary Efficacy	
• To demonstrate the efficacy of a 3-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by the HQ-CT.	• Change from baseline to the end of the 3-month Core Period in HQ-CT total score.

Secondary Efficacy	
• To demonstrate the efficacy of 3-month treatment with livoletide as compared to placebo for: o Reducing total body fat mass in overweight/obese patients with PWS; o Reducing WC in overweight/obese patients with PWS; o Reducing BW in overweight/obese patients with PWS.	o Percentage change from baseline to the end of the 3-month Core Period in total body fat mass in overweight/obese patients with PWS; o Change from baseline to the end of the 3-month Core Period in WC in overweight/obese patients with PWS; o Percentage change from baseline to the end of the 3-month Core Period in BW in overweight/obese patients with PWS.
Safety	
• To assess the safety and tolerability of livoletide as compared to placebo over a 3-month treatment period.	• Incidence of AEs; • Vital signs; • Height and BMI; • Physical examination; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).
Pharmacokinetics	
• To characterize plasma PK of livoletide in patients with PWS.	• The PK endpoints will be described in details in the SAP and will include as the data allow: C_{max}, T_{max}, AUC_{0-4}, and other PK parameters of livoletide
Additional Assessments	
• To evaluate the effect of livoletide as compared to placebo on: o Hyperphagia severity as assessed by the CgGIS-H and CGIS-H; o Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H; o Clinical global impression of change as assessed by the CGI-I; o Clinical global impression of severity as assessed by the CGI-S; o Fasting (for approximately 8 hours) and postprandial glucose and insulin (profile); o Patient-reported appetite following breakfast as assessed by an NRS;	• Change from baseline in: o CgGIS-H and CGIS-H scores; o CgGIC-H and CGIC-H scores; o CGI-I score; o CGI-S score; o Fasting (for approximately 8 hours) and postprandial glucose and insulin measurement (profile); o Appetite-NRS score;
o Patients' Non-Food-Related behaviors as assessed by the DBC2-P; o Patients' Quality of Life as assessed by the PedsQL™ 4.0 Generic Core Scales; o Caregivers' disease burden as assessed by the ZBI; o Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1;	o DBC2-P score; o PedsQL™ 4.0 Parent-Proxy age-appropriate Reports score; o ZBI score; o EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score;
• To evaluate the measurement properties of HQ-CT in the study population (test-retest reliability, construct validity and ability to detect change); • To derive the responder threshold for meaningful change in the HQ-CT; • To compare the number of HQ-CT responders between groups	• Evaluation of the measurement properties and interpretation of clinically meaningful HQ-CT change in the study population using blinded study data and according to a psychometric analysis plan; • Responder definition using anchor-based methods supplemented with both CDF and PDF to derive the responder threshold for meaningful change; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.
PHASE 2B EXTENSION PERIOD	

Efficacy	
• To assess the maintenance of efficacy of livoletide treatment on caregiver-observed food-related behavior as assessed by the HQ-CT; • To assess the maintenance of efficacy of livoletide treatment on total body fat mass, WC, and BW in overweight/obese patients with PWS.	• Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in HQ-CT total score; • Percentage change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in BW in overweight/obese patients with PWS.
Safety	
• To assess the long-term safety and tolerability of livoletide over a 12-month treatment period.	• Incidence of AEs; • Vital signs; • Height and BMI; • Physical examination; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).
Pharmacokinetics	
• To characterize the plasma PK of livoletide in patients with PWS; • To characterize the plasma PK profile of livoletide in a subset of patients with PWS	Plasma livoletide PK parameters will be derived using non-compartmental methods. Where possible, the following PK parameters will be determined. Additional parameters may also be calculated as appropriate. C_{max}; t_{max}; C_{min}; t_{min}; C_{avg}; FI; $AUC_{(0\text{-}tau)}$; λz; $t_{1/2}$; CL/F; Vz/F; $RAUC_{(0\text{-}tau)}$; RC_{max}; and LI as appropriate.
Additional Assessments	
• To evaluate the long-term effect of livoletide on: o Hyperphagia severity as assessed by the CgGIS-H and CGIS-H, respectively; o Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H, respectively; o Clinical global impression of change as assessed by the CGI-I; o Clinical global severity as assessed by the CGI-S; o Fasting (for approximately 8 hours) glucose and insulin; o Patients' Non-Food-Related behaviors as assessed by the DBC2-P version; o Patients' Quality of Life as assessed by the PedsQL™ 4.0 Generic Core Scales; o Caregiver disease burden as assessed by the ZBI; o Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1.	• Change from baseline in: o CgGIS-H and CGIS-H scores; o CgGIC-H and CGIC-H scores; o CGI-I score; o CGI-S score; o Fasting (for approximately 8 hours) glucose and insulin measurement; o DBC2-P score; o PedsQL™ Parent-Proxy age-appropriate Reports score; o ZBI score; o EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.

Table 2: Phase 2b – Description of the study objectives and endpoints for the Core Period and the Extension Period

Abbreviations: λz=apparent terminal rate constant; ADA=anti-drug antibodies; AEs=adverse events; $AUC_{(0\text{-}tau)}$=area under the concentration-time curve during the dosing interval; BMI=body mass index; BW=body weight; C_{avg}=average concentration during the dosing interval; CDF=cumulative distribution function; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; CL/F=apparent total body clearance; C_{max}=maximum concentration; C_{min}=observed minimum concentration; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; FI=fluctuation index over the dosing interval; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for Clinical Trials; IGF-1=insulin-like growth factor-1; LI=linearity index; NRS=Numerical Rating Scale; PDF=probability density function; PK=pharmacokinetic; PedsQL™=Pediatric Quality of Life inventory™; PWS=Prader-Willi syndrome; $RAUC_{(0\text{-}tau)}$=accumulation ratio for $AUC_{(0\text{-}tau)}$; RC_{max}=accumulation ratio for C_{max}; $t_{1/2}$=apparent terminal half-life; t_{max}=time of C_{max}; t_{min}=time of C_{min}; Vz/F=apparent volume of distribution; WC=waist circumference; ZBI=Zarit Burden Interview.

3.1.2 Phase 3 Tabular Summary of Trial Objectives and Endpoints

OBJECTIVES	ENDPOINTS
PHASE 3 CORE PERIOD	
Primary Efficacy	
• To demonstrate the efficacy of a 6-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by the HQ-CT.	• Change from baseline to the end of the 6-month Core Period in HQ-CT total score.
Secondary Efficacy	
• To demonstrate the efficacy of 6-month treatment with livoletide as compared to placebo for: o Reducing total body fat mass in overweight/obese patients with PWS; o Reducing WC in overweight/obese patients with PWS; o Reducing BW in overweight/obese patients with PWS.	o Percentage change from baseline to the end of the 6-month Core Period in total body fat mass in overweight/obese patients with PWS; o Change from baseline to the end of the 6-month Core Period in WC in overweight/obese patients with PWS; o Percentage change from baseline to the end of the 6-month Core Period in BW in overweight/obese patients with PWS.
Safety	
• To assess the safety and tolerability of livoletide as compared to placebo over a 6-month treatment period.	• Incidence of AEs; • Vital signs; • Height and BMI; • Physical examination; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).
Additional Assessments	
• To evaluate the effect of livoletide as compared to placebo on: o Hyperphagia severity as assessed by the CgGIS-H and CGIS-H; o Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H; o Clinical global impression of change as assessed by the CGI-I; o Clinical global impression of severity as assessed by the CGI-S; o Fasting (for approximately 8 hours) and postprandial glucose and insulin (profile); o Patient-reported appetite following breakfast as assessed by	• Change from baseline in: o CgGIS-H and CGIS-H scores; o CgGIC-H and CGIC-H scores; o CGI-I score; o CGI-S score; o Fasting (for approximately 8 hours) and postprandial glucose and insulin measurement (profile); o Appetite-NRS score;

OBJECTIVES	ENDPOINTS
an NRS; o Patients' Non-Food-Related behaviors as assessed by the DBC2-P; o Patients' Quality of Life as assessed by the PedsQL™ 4.0 Generic Core Scales; o Caregivers' disease burden as assessed by the ZBI; o Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1; • To compare the number of HQ-CT responders between groups	o DBC2-P score; o PedsQL™ 4.0 Parent-Proxy age-appropriate Reports score; o ZBI score; o EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.

OBJECTIVES	ENDPOINTS
PHASE 3 EXTENSION PERIOD	
Efficacy	
• To assess the maintenance of efficacy of livoletide treatment on caregiver-observed food-related behavior as assessed by the HQ-CT; • To assess the maintenance of efficacy of livoletide treatment on total body fat mass, WC, and BW in overweight/obese patients with PWS.	• Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in HQ-CT total score; • Percentage change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in total body fat mass in overweight/obese patients with PWS; • Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in WC in overweight/obese patients with PWS; • Percentage change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in BW in overweight/obese patients with PWS.
Safety	
• To assess the long-term safety and tolerability of livoletide over a 12-month treatment period.	• Incidence of AEs; • Vital signs; • Height and BMI; • Physical examination; • Lean body mass and bone mineral density; • ECG; • Safety laboratory parameters (clinical chemistry including lipids, coagulation, hematology, urinalysis, HbA1c, ghrelin, ADA, and IGF-1).
Additional Assessments	
• To evaluate the long-term effect of livoletide on: o Hyperphagia severity as assessed by the CgGIS-H and CGIS-H, respectively; o Hyperphagia global impression of change as assessed by the CgGIC-H and CGIC-H, respectively; o Clinical global impression of change as assessed by the CGI-I; o Clinical global severity as assessed by the CGI-S; o Fasting (for approximately 8 hours) glucose and insulin; o Patients' Non-Food-Related behaviors as assessed by the DBC2-P version; o Patients' Quality of Life as assessed by the PedsQL™ 4.0 Generic Core Scales; o Caregiver disease burden as assessed by the ZBI; o Health state utilities as assessed by EQ-5D-5L Self-complete version and Proxy version 1.	• Change from baseline in: o CgGIS-H and CGIS-H scores; o CgGIC-H and CGIC-H scores; o CGI-I score; o CGI-S score; o Fasting (for approximately 8 hours) glucose and insulin measurement; o DBC2-P score; o PedsQL™ Parent-Proxy age-appropriate Reports score; o ZBI score; o EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score; • Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.

Table 3: Phase 3 – Description of the study objectives and endpoints for the Core Period and the Extension Period

Abbreviations: ADA=anti-drug antibodies; AEs=adverse events; BMI=body mass index; BW=body weight; CgGIC-H=Caregiver Global Impression of Change – Hyperphagia; CgGIS-H=Caregiver Global Impression of Severity – Hyperphagia; CGIC-H=Clinical Global Impression of Change – Hyperphagia; CGI-I=Clinical Global Impression of Improvement; CGI-S=Clinical Global Impression of Severity; CGIS-H=Clinical Global Impression of Severity – Hyperphagia; DBC2-P=Developmental Behavior Checklist 2-Parent/Carer version; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life Five Dimension Five Level Scale; HbA1c=glycated hemoglobin; HQ-CT=Hyperphagia Questionnaire for

Clinical Trials; IGF-1=insulin-like growth factor-1; NRS=Numerical Rating Scale; PedsQL™=Pediatric Quality of Life inventory™; PWS=Prader-Willi syndrome; WC=waist circumference; ZBI=Zarit Burden Interview.

3.2 Justification for Core Period Primary and Secondary Endpoints

3.2.1 Phase 2b Justification for Core Period Primary and Secondary Endpoints

In Phase 2b, the 3-month time point provides a reasonable balance between observing a treatment effect in food-related behavior and minimizing dropouts.

3.2.1.1 Phase 2b Primary Endpoint

The primary endpoint proposed for Phase 2b with livoletide is the change from baseline to the end of the 3-month Core Period for Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score (see Section 19.2 Appendix B for HQ-CT content).

The HQ-CT is derived from the HQ, a 13-item disease-specific questionnaire that was designed to assess food-related behaviors in patients with PWS as reported by caregivers as patients with PWS are unable to consistently and reliably report the severity of their hyperphagia and preoccupation with food, and food related behaviors (61).

The HQ-CT is a 9-item instrument that has been developed and validated for use in clinical trials (content validity and measurement properties) based on industry standard and regulatory guidance (63). The HQ-CT was initially developed in US English and has been subsequently culturally adapted in 10 European languages (64). All items on the HQ-CT are rated on a five-point scale and are summed to generate a total score (0 to 36).

Change in the HQ-CT total score is considered by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) as a valid primary endpoint for use in clinical trials to demonstrate efficacy of a study drug in hyperphagia associated with PWS (based on discussions the Sponsor had at pre-IND and scientific advice meetings with FDA and EMA, respectively).

3.2.1.2 Phase 2b Secondary Endpoints (Core Period)

The secondary endpoints proposed for Phase 2b Core Period are:

- Percentage change from baseline to the end of the 3-month Core Period in total body fat mass in overweight/obese patients with PWS;
- Change from baseline to the end of the 3-month Core Period in WC in overweight/obese patients with PWS;
- Percentage change from baseline to the end of the 3-month Core Period in BW in overweight/obese patients with PWS.

Overweight and obesity is defined here as:

- For adults: Body mass index (BMI) is ≥27 kg/m^2;
- For patients ≥ 4 and <18 years of age: ≥90^{th} percentile for the same age and sex.

All parameters are relevant in clinical practice on weight management. Waist circumference is used as an indirect measure of visceral fat content and cardiovascular risk.

3.2.2 Phase 3 Justification for Core Period Primary and Secondary Endpoints

The Phase 3 Core Period primary and secondary endpoints are the same as for Phase 2b but will be determined at 6 months. The 6-month time point allows for an assessment of longer-term,

placebo-controlled endpoints that may require more than 3 months to observe a clinically meaningful effect. For example, some metabolic endpoints such as body composition and glycemic parameters may require a longer exposure period to observe maximal effects.

4 STUDY DESIGN

4.1 Overall Study Design

The proposed Phase 2b/3 study will evaluate the safety, tolerability, and effects of livoletide on food-related behaviors in patients with PWS.

This protocol includes 2 consecutive parts:

1. The first part is a Phase 2b dose-response study consisting of a 3-month double-blind, placebo-controlled Core Period and a 9-month Extension Period.
2. The second part is a Phase 3 study consisting of a 6-month double-blind, placebo-controlled Core Period followed by a 6-month Extension Period. Phase 3 may be initiated following review of safety and efficacy results at the completion of the Phase 2b Core Period.

Patients who enrolled in the Phase 2b part will not be eligible for recruitment in the Phase 3 part. The overall study duration for each patient, inclusive of screening and follow-up will be approximately 14 months (same duration for Phase 2b and Phase 3).

4.1.1 Phase 2b Overall Study Design

The Phase 2b part of the study will include adult and pediatric patients (4-65 years of age) with genetically confirmed PWS and evidence of hyperphagia as judged by the investigator and HQ-CT total score ≥10.

Phase 2b will include:

- **Phase 2b Core Period:** A 3-month, double-blind, randomized, placebo-controlled treatment period (Phase 2b Core Period). After a screening period (up to 4 weeks), eligible patients will be randomized in a 1:1:1 ratio to one of two livoletide doses (8 mg/mL, low exposure or 16 mg/mL, high exposure) or placebo.

  Randomization will be stratified based on age (≥ 4 and < 8 years of age, ≥ 8 and <18 years of age and ≥18 years of age) and BMI (patients ≥18 years of age: BMI <27 kg/m^2 vs BMI ≥27 kg/m^2; patients 4-17 years of age: BMI <90th percentile vs BMI ≥90th percentile for the same age and sex). For details on the stratification, please refer to Section 13.6;

- **Phase 2b Extension Period:** A 9-month Extension Period. Patients randomized to livoletide for the Core Period will remain on the randomized dose (i.e. 8 mg/mL, low exposure or 16 mg/mL, high exposure) during the Extension Period. Patients randomized to placebo for the Core Period will cross-over to livoletide low or high exposure in a randomized (1:1) manner. The Interactive Response Technology (IRT) will manage treatment assignment so that the double-blind status can remain intact at the start of the Extension Period.

The overall study design and timelines for Phase 2b are presented in Figure 6.

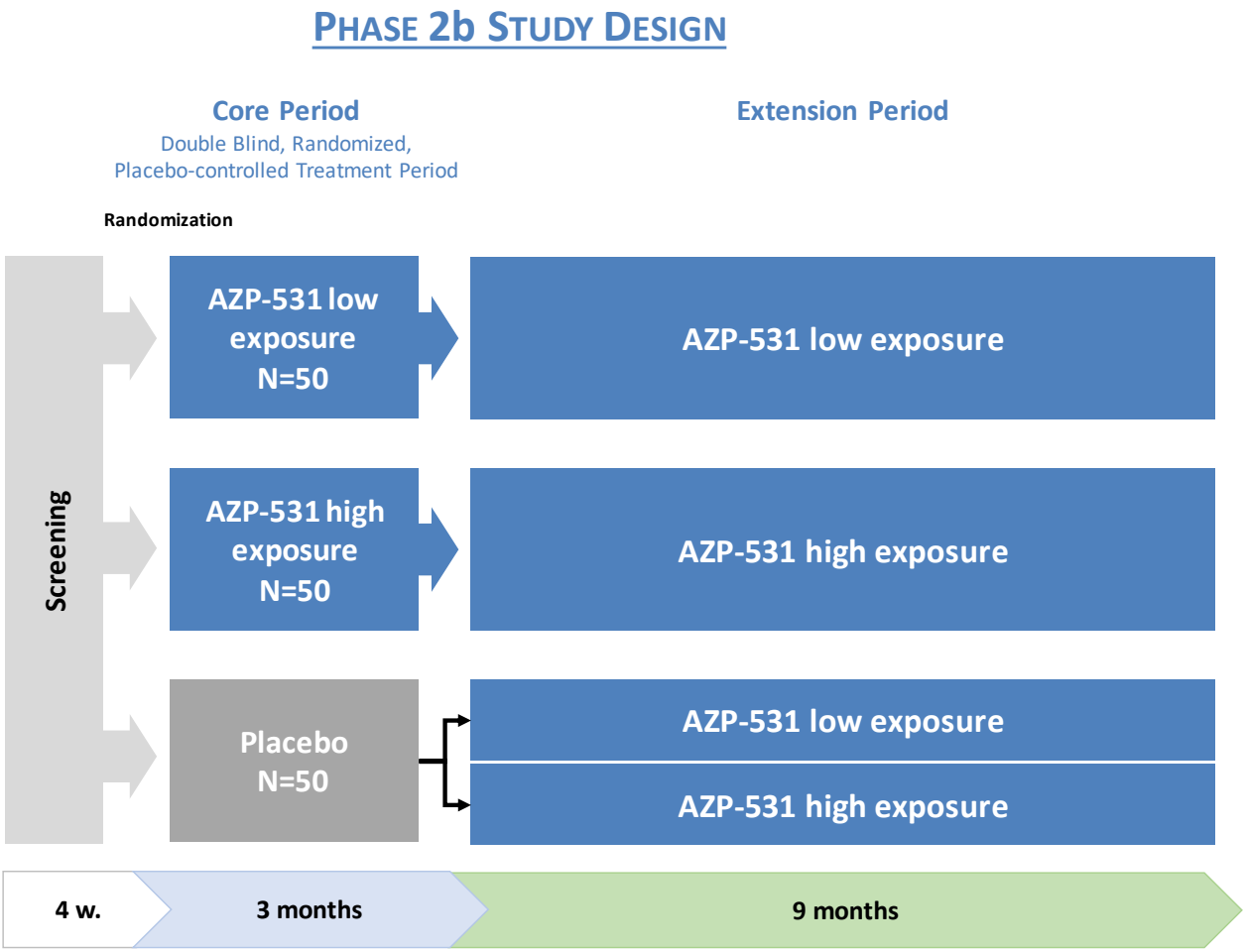


Figure 6: Phase 2b Core and Extension Periods–Study Schematic

Abbreviations: AZP-531=livoletide; N=number of patients; w=weeks.

4.1.2 Phase 3 Overall Study Design

Phase 3 may commence after completion of Phase 2b Core Period. Following review of data at the completion of the Phase 2b Core Period, the Phase 3 livoletide doses will be reassessed along with the statistical assumptions. Patients who enrolled in the Phase 2b part will not be eligible for recruitment in the Phase 3 part.

The Phase 3 part of the study will include adult and pediatric patients (8-65 years of age, 4-7 years of age may also be included) with genetically confirmed PWS and evidence of hyperphagia as judged by the investigator and HQ-CT total score ≥10.

Phase 3 will include:

- **Phase 3 Core Period:** A 6-month, double-blind, randomized, placebo-controlled treatment period. After a screening period (up to 4 weeks), eligible patients will be randomized to livoletide or placebo;
- **Phase 3 Extension Period:** A 6-month Extension Period. Patients randomized to livoletide for the Core Period will remain on the randomized dose during the Extension Period. Patients randomized to placebo for the Core Period will cross-over to livoletide during the Extension Period. The IRT will manage treatment assignment so that the double-blind status can remain intact at the start of the Extension Period.

The overall study design and timelines for Phase 3 are presented in Figure 7.

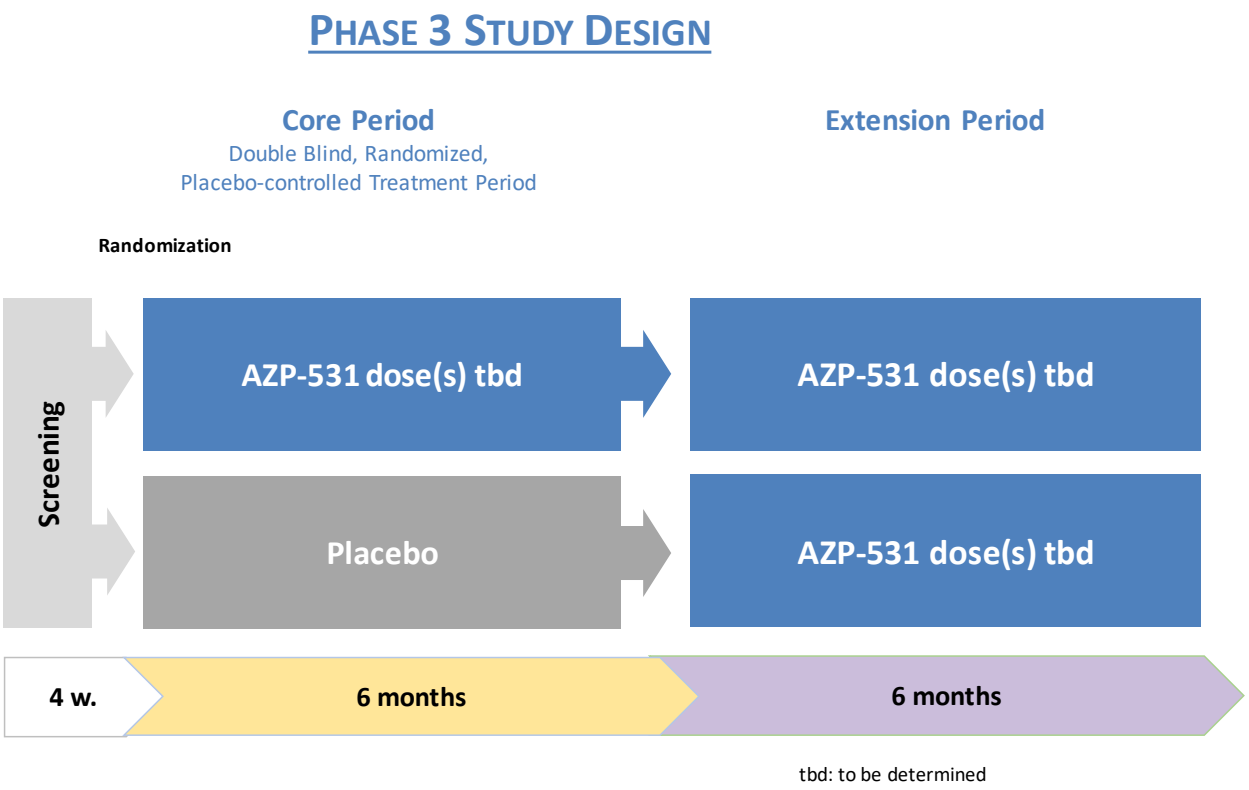


Figure 7: Phase 3 Core and Extension Periods–Study Schematic

Abbreviations: AZP-531=livoletide; tbd=to be determined; w=weeks.

4.2 Scientific Rationale and Discussion for Study Design

4.2.1 Rationale for the Extension Period

Prader-Willi syndrome is a life-long disease. Therefore, it is critical to assess whether an effect on food behavior is maintained and that no compensatory mechanism that would decrease efficacy over time appears.

In order to assess the maintenance of efficacy of livoletide treatment, Phase 2b will include a 9-month Extension Period following the 3-month Core Period and Phase 3 will include a 6-month Extension Period following the 6-month Core Period. For both Phase 2b and Phase 3 the combined Core Period and Extension Period will allow collection of safety data over 12 months of treatment.

4.2.2 Rationale for the Control Arm

The control arm that has been selected for both the Phase 2b Core Period and Phase 3 Core Period is placebo. A placebo-controlled study was chosen because there is no approved medication for the pharmacological treatment of hyperphagia in patients with PWS that could have been used as an active comparator.

4.3 Justification for Dose

The low exposure (8 mg/mL, 60 µg/kg/day targeted exposure) and high exposure (16 mg/mL, 120 µg/kg/day targeted exposure) daily doses have been selected for Phase 2b in order to assess dose effect relationship.

The selection of the doses is supported by the following observations:

- Cumulative nonclinical data available to date indicate that livoletide has a wide safety margin. In rats and dogs, the highest chronic dose (13 weeks) tested was considered the No Observed Adverse Effect Level (NOAEL) and provided a group mean AUC value of greater than or equal to 50-fold of the high clinical exposure;
- Administration of livoletide was well tolerated in humans following a single administration at doses up to 120 µg/kg and following repeated administration for 14 days at doses up to 60 µg/kg/day;
- PK characteristics of livoletide were comparable overall at the same doses in 3 study populations including healthy subjects, obese subjects, and patients with T2D. Following repeated administration up to 60µg/kg/day, C_{max}, and AUCs were dose-related and increased proportionally with the dose administered;
- Phase 2a clinical data obtained in patients with PWS demonstrated efficacy and a good safety profile when livoletide was administered once a day for 14 days (60 µg/kg/day targeted exposure).

Following review of data at the completion of the Phase 2b Core Period, the Phase 3 livoletide doses will be reassessed along with the statistical assumptions.

4.4 Number of Patients

For **Phase 2b**, approximately one hundred and fifty (150) patients (8 to 65 years of age) will be randomized in a 1:1:1 ratio to one of the 3 arms (livoletide low exposure [8 mg/mL], livoletide

high exposure [16 mg/mL], or placebo). In addition to this cohort of 150 patients, a separate cohort of patients 4 to 7 years of age will be randomized similarly (1:1:1 ratio). Please refer to Section 13.2 for details about the determination of the number of patients.

For **Phase 3**, the total number of required patients to be randomized is estimated to be 50 patients per group. Final sample size will be determined following analysis of data at the completion of the Phase 2b Core Period.

4.5 Number of Study Sites

This study will be conducted at multiple centers worldwide, at approximately 40 centers in Europe, Australia and North America. Participating sites will be specialized in the management of patients with PWS.

4.6 Definition of the End of the Study

The end of study is defined as the last visit of the last patient (LPLV) in the trial globally.

5 STUDY POPULATION

5.1 Phase 2b Patient Inclusion and Exclusion Criteria

5.1.1 Phase 2b Patient Inclusion Criteria for the Core Period

A patient must meet ALL of the following inclusion criteria at screening in order to be eligible to participate in the study:

1. A confirmed genetic diagnosis of PWS. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If the PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria.
2. Male and female patients 4 to 65 years of age, inclusive, 12 to 65 years for Australian sites 201 and 202.
3. Have evidence of increased appetite or hyperphagia, as judged by the investigator, and a total HQ-CT score ≥10 (scale of 0-36).
4. Patients willing to comply with the following lifestyle considerations:
    a. Be on a stable diet regimen.
    b. Be on a stable physical activity regimen. Patients should agree to refrain from changing their usual level of physical activity.
5. Each patient must have a single primary caregiver who will be able to evaluate and score that patient's behaviors and perform any study-related activities as defined in the protocol throughout the study. That person must have been caring for the patient for at least 6 months prior to screening, spend, on average, approximately 4 (or more) waking hours per day with the patient, and should be available for the duration of the study.
        a. During the Extension Period, the time spent by the caregiver with the patient may be reduced, as long as the caregiver spends, on average, approximately 4 (or more) waking hours per day with the patient at least 2 weeks before each visit.

6. BMI ≤65 kg/m^2 for adult patients.
7. WCBP must have a negative pregnancy test.
8. All WCBP, sexually active male patients, and all opposite sex partners of patients should agree to use medically-approved effective methods of birth control (e.g. diaphragm, condoms with spermicide) throughout the study and for 30 days after the last dose of study drug.
    a. WCBP or male patients who agree with a true abstinence (when in line with the preferred or usual lifestyle of the patient) can be included.
9. Adequate renal function, defined as serum creatinine ≤1.5 × upper limit of normal (ULN).
10. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤3 × ULN.
11. Diabetes medications will be permitted if doses have been stable for at least 3 months prior to screening. Insulin doses are considered to have been stable if the prescribed total daily insulin doses are within approximately 20% of those at screening.
12. Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening.
13. Psychotropic treatment (e.g. modafinil, topiramate, zonisamide, fluoxetine, aripiprazole, risperidone, quetiapine, and benzodiazepines) will be permitted if doses have been stable for at least 2 months prior to screening.
14. Any other medication that is likely to affect behavior, body composition, or lipids (in the opinion of the investigator) (must be stable for at least 2 months prior to screening, except as noted below:
    a. Thyroid hormone: changes within approximately 13 µg/day are acceptable
    b. Sex steroids: patients on sex steroids must have been taking them for at least 2 months at screening; dose changes within approximately 25% of the screening dose are acceptable as are changes within a class (e.g., from one oral contraceptive to another, or from one selective estrogen receptor to another).
15. Approved informed consent (Assent form for patients under the age of majority) signed by the patient, parent, or legal guardian, as appropriate, at the screening visit before any study procedures.
16. **For patients from France only**: Is either affiliated with or a beneficiary of "sécurité sociale".

5.1.2 Phase 2b Patient Exclusion Criteria

All patients meeting any of the following exclusion criteria at screening will be excluded from participation in this study:

1. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspected alcohol abuse.

2. History of significant cardiovascular disease including history of congestive heart failure (CHF, New York Heart Association [NYHA] Class 3 or 4), angina pectoris, or myocardial infarction (MI) within 6 months prior to screening.
3. Type 1 diabetes mellitus.
4. HbA1c >10%.
5. History of frequent hypoglycemia.
6. Blood pressure systolic >160 mmHg, diastolic >90 mmHg (adult patients) and blood pressure systolic >140 mmHg, diastolic >90 mmHg (patients 4 to 17 years of age).
7. Use of weight loss agents and medications taken to affect appetite (e.g. Orlistat®, Lorcaserin, Qsymia®, Contrave®/Mysimba®, glucagon-like-peptide 1 [GLP-1] analogs, as well as any over-the counter medication and herbal agent) within 2 months prior to screening.
8. Co-morbid condition or disease (such as respiratory disease or psychiatric disorder) diagnosed less than 1 month prior to screening.
9. Co-morbid condition or disease or abnormal laboratory finding that would in the investigator's judgment increase the patient risk to participating in this study or that will not allow the patient to complete the study.
10. Known history of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
11. Participation in a clinical trial with an investigational agent within 3 months prior to screening.
12. Clinically significant abnormalities on ECG at screening, as follows:
    a. Patients 4 years of age: males QT interval corrected for heart rate by Bazett's formula (QTcB) >448 ms, females QTcB >442 ms.
    b. Patients 5 to 7 years of age: males QTcB >443 ms, females QTcB >449 ms.
    c. Patients 8 to 11 years of age: males (QTcB) >440 ms, females QTcB >447 ms.
    d. Patients 12 to 15 years of age: males QTcB >449 ms, females QTcB >457 ms.
    e. Patients ≥16 years of age: males QTcB >450 ms, females QTcB >470 ms.
13. Pregnant or lactating woman.
14. History of hypersensitivity to drugs with a similar chemical structure or class as livoletide (AG and UAG).
15. Unwillingness or inability to follow the procedures outlined in the protocol.
16. Patients living in a group home ≥50% of the time.
17. Patients with body weight <20 kg.

5.1.3 Phase 2b Patient Inclusion Criteria for the Extension Period

In order to be able to participate in the Extension Period, patients will be required to have completed the Core Period.

5.2 Phase 3 Patient Inclusion and Exclusion Criteria

Based on results from Phase 2b, some inclusion criteria for the Phase 3 Core and Extension Periods may be adjusted.

5.2.1 Phase 3 Patient Inclusion Criteria for the Core Period

A patient must meet ALL of the following inclusion criteria at screening in order to be eligible to participate in the study:

1. A confirmed genetic diagnosis of PWS. Documentation of PWS subtype (chromosome 15 micro-deletion *versus* non-deletion) is also required for the study. If the PWS subtype is not known, a sample for testing may be obtained and the patient may continue on to be enrolled into the study if he or she meets all the other inclusion criteria and none of the exclusion criteria.
2. Male and female patients 8 to 65 years of age, inclusive.
3. Have evidence of increased appetite or hyperphagia, as judged by the investigator, and a total HQ-CT score ≥10 (scale of 0-36).
4. Patients willing to comply with the following lifestyle considerations:
    a. Be on a stable diet regimen.
    b. Be on a stable physical activity regimen. Patients should agree to refrain from changing their usual level of physical activity.
5. Each patient must have a single primary caregiver who will be able to evaluate and score that patient's behaviors and perform any study-related activities as defined in the protocol throughout the study. That person must have been caring for the patient for at least 6 months prior to screening, spend, on average, approximately 4 (or more) waking hours per day with the patient, and should be available for the duration of the study.
        a. During the Extension Period, the time spent by the caregiver with the patient may be reduced as long as the caregiver spends, on average, approximately 4 (or more) waking hours per day with the patient at least 2 weeks before each visit.
6. BMI ≤65 kg/m^2 for adult patients.
7. WCBP must have a negative pregnancy test.
8. All WCBP, sexually active male patients, and all opposite sex partners of patients should agree to use medically-approved effective methods of birth control (diaphragm, condoms with spermicide) throughout the study and for 30 days after the last dose of study drug.
        a. WCBP or male patients who agree with a true abstinence (when in line with the preferred or usual lifestyle of the patient) can be included.
9. Adequate renal function, defined as serum creatinine ≤1.5 × ULN.
10. Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN and AST and ALT levels ≤3 × ULN.
11. Diabetes medications will be permitted if doses have been stable for at least 3 months prior to screening. Insulin doses are considered to have been stable if the prescribed total daily insulin doses are within approximately 20% of those at screening.

12. Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening.
13. Psychotropic treatment (e.g. modafinil, topiramate, zonisamide, fluoxetine, aripiprazole, risperidone, quetiapine, and benzodiazepines) will be permitted if doses have been stable for at least 2 months prior to screening.
14. Any other medication that is likely to affect behavior, body composition, or lipids (in the opinion of the investigator) must be stable for at least 2 months prior to screening, except as noted below:
    a. Thyroid hormone: changes within approximately 13 µg/day are acceptable
    b. Sex steroids: patients on sex steroids must have been taking them for at least 2 months at screening; dose changes within approximately 25% of the screening dose are acceptable as are changes within a class (e.g., from one oral contraceptive to another, or from one selective estrogen receptor to another).
15. Approved informed consent (Assent form for patients under the age of majority) signed by the patient, parent, or legal guardian, as appropriate, at the screening visit before any study procedures.
16. **For patients from France only**: Is either affiliated with or a beneficiary of "sécurité sociale".

5.2.2 Phase 3 Patient Exclusion Criteria

A patient who enrolled in the Phase 2b part is not eligible for recruitment in the Phase 3 part.

All patients meeting any of the following exclusion criteria at screening will be excluded from participation in this study:

1. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspected alcohol abuse.
2. History of significant cardiovascular disease including history of CHF (NYHA Class 3 or 4), angina pectoris, or MI within 6 months prior to screening.
3. Type 1 diabetes mellitus.
4. HbA1c >10%.
5. History of frequent hypoglycemia.
6. Blood pressure systolic >160 mmHg, diastolic >90 mmHg (adult patients) and blood pressure systolic >140 mmHg, diastolic >90 mmHg (patients 8 to 17 years of age).
7. Use of weight loss agents and medications taken to affect appetite (e.g. Orlistat®, Lorcaserin, Qsymia®, Contrave®/Mysimba®, GLP-1 analogs, as well as any over-the counter medication and herbal agent) within 2 months prior to screening.
8. Co-morbid condition or disease (such as respiratory disease or psychiatric disorder) diagnosed less than 1 month prior to screening.

9. Co-morbid condition or disease or abnormal laboratory finding that would in the investigator's judgment increase the patient risk to participating in this study or that will not allow the patient to complete the study.
10. Known history of hepatitis B, hepatitis C, or HIV.
11. Participation in a clinical trial with an investigational agent within 3 months prior to screening.
12. Patients who participated in the Phase 2b part of the study.
13. Clinically significant abnormalities on ECG at screening, as follows:
    a. Patients 8 to 11 years of age: males QTcB >440 ms, females QTcB >447 ms.
    b. Patients 12 to 15 years of age: males QTcB >449 ms, females QTcB >457 ms.
    c. Patients ≥16 years of age: males QTcB >450 ms, females QTcB >470 ms.
14. Pregnant or lactating woman.
15. History of hypersensitivity to drugs with a similar chemical structure or class as livoletide (AG and UAG).
16. Unwillingness or inability to follow the procedures outlined in the protocol.
17. Patients living in a group home ≥50% of the time.
18. Patients with body weight <20 kg.

5.2.3 Phase 3 Patient Inclusion Criteria for the Extension Period

In order to be able to participate in the Extension Period, patients will be required to have completed the Core Period.

5.3 Lifestyle Considerations

5.3.1 Contraception Requirements

All patients of childbearing potential, if not abstinent, must be willing to practice effective contraception from the time of signing the informed consent form (ICF), during study treatment, and for 30 days after the final dose of study treatment. This includes sexually active male patients and all opposite sex partners of patients. Pediatric/adolescent patients must initiate contraception at menarche/spermarche or must discontinue study drug.

Please refer to Section 8.1.2.2 for the definition of childbearing potential.

5.3.2 Other Requirements or Considerations

During this study, patients are:

- Required to fast for approximately 8 hours before visits requiring blood sampling;
- Patients 8 to 65 years are required to take an isocaloric breakfast prepared at the study center at selected site visits.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study drug or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

In accordance with HQ-CT administration guidelines, individuals who do not meet the criterion for participation in the Phase 2b part of the protocol (screen failure) because of their HQ-CT score must not be rescreened for Phase 2b. However, given the length of time anticipated between closure of screening for Phase 2b and start of screening for Phase 3, such a patient may be eligible to screen for participation in Phase 3.

5.5 Justification for Inclusion of Vulnerable Participants

Although the research will include adults, both legally competent and under guardianship, we believe there is a clear clinical and methodological rationale for the inclusion of minors and patients under guardianship in this study:

1. Hyperphagia and abnormal food behavior start at an early age and are particularly critical in the management of patients with PWS.

   Considering i) the serious nature of hyperphagia, ii) the implementation of measures when hyperphagia starts to develop may be critical, and iii) safety and efficacy results from previous clinical studies, there is a reasonable likelihood that pediatric patients (children and adolescents) stand to benefit from the results of the research.

2. PWS is rare genetic disease with a limited population. Legal guardianship and assisted living are usually required to ensure a safe living environment, since individuals with PWS typically make poor decisions related to living arrangements and food (65, 66). A significant proportion of adult patients with PWS are under guardianship. For example, in France, 52.8% of patients with PWS are under guardianship (67).

   Considering the challenging number of available patients in this rare disease, and in order have reliable results, patients under guardianship measures will also be enrolled in this study.

Overall, based on clinical results from the Phase 2a study, patients participating in this study may benefit from the study treatment. It is reasonable to assume that the research is necessary to promote the health of the population represented and this research cannot instead be performed only on legally competent persons.

6 STUDY DRUGS

6.1 Study Drug Administration

6.1.1 Study Drug Description

Information on the study drugs (livoletide and placebo product) can be obtained from the IB for livoletide.

6.1.2 Dosing and Administration

Study drug must be dispensed or administered only to patients enrolled in the study and in accordance with the protocol.

Study drug doses will be administered by the site staff during site visits. Otherwise, other doses (doses in between site visits) will be administered at the patient's home (or other location convenient to the patient). Injections will be performed each study morning before breakfast at approximately the same time. At the randomization visit the injection will be performed when all the assessments have been completed. At selected site visits, an isocaloric breakfast will be served 30 minutes following injection.

Study drug will be administered by SC injection at rotating sites on the abdomen. Study drug must be kept refrigerated at 2 to 8°C (36 to 46°F).

The inclusion criterion age range of 4 to 65 years is expected to correspond to a BW range of ~20 to 140 kg. Therefore, livoletide will be dosed according to BW on a µg/kg basis and will be provided as a sterile liquid formulation (in 0.9% sodium chloride [NaCl] solution) in single-use clear glass vials. Two concentrations of livoletide will be available for this study, 8 mg/mL and 16 mg/mL. The volume of dosing will be adjusted according to BW (Table 4) to achieve targeted livoletide exposure levels of approximately 60 µg/kg and 120 µg/kg (i.e. a low exposure and a high exposure). Both livoletide concentrations as well as matching placebo are identical in appearance to maintain the study blind. Placebo will be administered at the same volumes as livoletide.

	Low exposure (8 mg/mL)	**High exposure (16 mg/mL)**
Body weight range (kg)	**Daily injection volume (mL)**	**Daily injection volume (mL)**
20.0 to 29.0	0.125	0.125
30.0 to 49.0	0.250	0.250
50.0 to 70.0	0.375	0.375
>70.0	0.500	0.500

Table 4: Adjustment of livoletide dosing according to body weight

The exposure dosing will be adjusted if there is any weight change at the 3-month visit at the end of the Core Period in Phase 2b or at the 6-month visit at the end of the Core Period in Phase 3.

Detailed instructions on study drug administration will be provided to the caregivers and site in a specific document.

6.1.2.1 Route of Administration

The study drug will be administered subcutaneously as a single injection under a full skin fold of the anterior abdominal region, at rotating sites, every day during the treatment period.

6.1.2.2 Starting Dose and Dose Escalation Schedule

Two exposure levels per dose (i.e. 60 µg/kg and 120 µg/kg) will be targeted in the study with each serving as starting dose. No dose escalation will be permitted during the study.

Following review of data at the completion of the Phase 2b Core Period, the Phase 3 livoletide doses will be reassessed along with the statistical assumptions.

6.1.2.3 Dose Adjustments/Modifications/Delays

If a dose is missed, it should not be taken if it is less than 8 hours until the next dose.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

6.2.1.1 Acquisition

Study drug will be dispensed to the study center in a blinded fashion as treatment kits. The allocation of study drug to patients must only be carried out by the IRT. For further information on this procedure, please refer to the dedicated manual.

Drug administration supplies will also be provided.

6.2.1.2 Accountability

The investigator has the ultimate responsibility for the study drug accountability at the study site. Each investigator/designated individual (e.g. pharmacist or any other appropriate person) is responsible for taking an inventory of each shipment of study drug received. The investigator/designee will acknowledge receipt of study drug, using IRT to confirm shipment condition and content.

Study drug must be used only as directed in this protocol. The investigator/designee must keep accurate records of all study drug received from Millendo Therapeutics/designee. Additionally, the investigator/designee must keep accurate records of the study drug throughout the study including the use by each patient, the reconciliation of all delivered and received study drug, and the return of used and unused study drug (as applicable) as specified in the dedicated manual. All study drugs must be accounted for and all discrepancies investigated and documented appropriately.

Study drug stock may not be removed from the investigative site where originally shipped without prior knowledge and consent of Millendo Therapeutics or their delegated Clinical Research Organization (CRO). When authorized, all applicable local, state, and national laws must be adhered to for the transfer.

At the end of the study, all used and unused vials of study drug will be destroyed by the investigative site or sent to a designated contractor for disposal on behalf of Millendo Therapeutics, per the instructions at that time.

6.2.2 Formulation, Appearance, Packaging, and Labeling

6.2.2.1 Pharmaceutical Formulation and Appearance

Livoletide and placebo will be manufactured by:

BAG Health Care GmbH
Amtsgerichtsstrasse 1-5
35423 Lich
Germany

Livoletide and placebo will be dispensed in same sized 2-mL clear single-use glass vials. Each livoletide vial will contain 0.6 mL of either the low concentration (8 mg/mL) or the high concentration (16 mg/mL) of sterile livoletide in 0.9% NaCl solution for injection. To ensure adequate blinding, all livoletide and placebo vials will be of comparable aspect at visual inspection.

6.2.2.2 Labeling and Packaging

All packaging, labeling, and the preparation of livoletide and placebo will be in compliance with GMP, as described in Annex 13 of Volume 4 to European Union GMP guidelines, and any other or local applicable regulations.

CSM Clinical Supplies Management Europe GmbH

Am Kronberger Hang 3

65824 Schwalbach a.Ts.

Germany

Study drug labels will include all appropriate local labeling requirements on the vial and external label. Sample labels will be submitted to health authorities, per local country submission requirements.

6.2.3 Product Storage and Stability

Treatment kits should be stored refrigerated (between +2°C and +8°C [(+36°F and +46°F]) either at the study center (locked environment with restricted access) or at patient's home, as applicable, prior to use.

No special procedures for the safe handling of study drug are required. A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Study drug supplied for this study may not be administered to any person not enrolled in the study.

6.2.4 Preparation

No preparation is required, the volume of the livoletide or placebo vial should be injected as it is. Instructions will be provided in a separate document.

6.3 Measures to Minimize Bias

6.3.1 Phase 2b Core Period Treatment Assignment and Blinding

Patients will be assigned to one of the 3 treatment groups in a randomized fashion. A computer-generated randomization schedule will be prepared prior to the start of the study. An IRT will be used to assign randomization number and kit number according to the randomization schedule.

Randomization will be 1:1:1 among treatment arms. Stratification will be performed based on age (≥ 4 and <8 years of age, ≥ 8 and <18 years of age, and ≥18 years of age) and BMI (patients ≥18 years of age: BMI <27 kg/m^2 vs BMI ≥27 kg/m^2; patients 4-17 years of age: BMI <90th percentile vs BMI ≥90th percentile for the same age and sex). A minimum of 25 overweight/obese subjects will be randomized per treatment group. Further details are described in Section 13.2.1.

Patients, investigational staff, and persons performing the assessments and data analysis will remain blinded to the identity of study treatment from the time of randomization until database lock.

The randomized code may be broken if an emergency situation arises that in the investigator's opinion requires the knowledge of the code (for example, life threatening situation or necessity to know the product administered to provide with the best medical care). The investigator must do his/her very best to contact the Sponsor or representative before unblinding the code through the IRT system. Date, time, and reason(s) for breaking the code must be recorded by the investigator.

Randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding. It is the responsibility of the investigator to maintain the blind throughout the study. At the conclusion of the trial, the occurrence of any emergency code breaks will be verified after return of all code break reports and unused drug supplies to the packaging supplier. The drug codes will be broken and made available (unblinding) for data analysis only when the clinical database is locked, and the protocol violations are determined.

The Sponsor reserves the right to break the blind for SAEs that are considered to be related to the study drug and unexpected, which could require an expedited report to the regulatory authorities.

6.3.2 Phase 2b Extension Period Treatment Assignment and Blinding

The IRT will manage treatment assignment for the Extension Period so that the double-blind status can remain intact at the start of the Extension Period. Thus, the Extension Period will remain double-blinded for a long as feasible to ensure as robust a dataset as possible. Change from baseline assessments within a given treatment arm, as well as comparisons between treatment arms, can still provide extremely valuable and meaningful data, especially if the blind in maintained. Patients randomized to livoletide for the Core Period will remain on the randomized dose during the Extension Period (i.e. a patient randomized to livoletide low exposure during the Core Period will remain on low exposure for the duration of the Extension Period, no changes are allowed). Patients randomized to placebo for the Core Period will cross-over to livoletide (low exposure [8 mg/mL] or high exposure [16 mg/mL] in a 1:1 randomized manner) during the Extension Period.

6.3.3 Phase 3 Treatment Assignment and Blinding

The same procedures used for Phase 2b will be used for Phase 3. Patients will be assigned to one of the treatment groups in a randomized fashion. A computer-generated randomization schedule will be prepared prior to the start of the study. An IRT will be used to assign randomization number and kit number according to the randomization schedule. Randomization and blinding procedures described for Phase 2b apply for Phase 3.

Stratification variables will be reassessed following review of data at the completion of the Phase 2b Core Period.

6.4 Tracking of Dose and Assessment of Patient Compliance

Compliance with study drug administration is dependent on administration of SC injections and attendance by the patient at the clinic for scheduled assessment visits. Compliance with study drug administration will be verified through observation by study staff, documented through the completion of a patient diary, and reported on the electronic case report forms (eCRFs).

6.5 Concomitant Therapies

All concomitant prescription medications taken during study participation will be recorded on the eCRFs. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications

For Phase 2b and 3, as described in Section 5.1 and Section 5.2, the following medications are allowed under specific conditions:

- **Diabetes Treatment:** Diabetes medication will be permitted if doses have been stable for at least 3 months prior to screening. Insulin doses are considered to have been stable if the prescribed total daily insulin doses are within approximately 20% of those at screening;
- **Growth Hormone Treatment:** Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening;
- **Psychotropic Treatment:** Psychotropic treatment (e.g. modafinil, topiramate, zonisamide, fluoxetine, aripiprazole, risperidone, quetiapine, and benzodiazepines) will be permitted if doses have been stable for at least 2 months prior to screening.

Any other medication that is likely to affect behavior, body composition, or lipids (in the opinion of the investigator) must be stable for at least 2 months prior to screening, except as noted below:

- Thyroid hormone: changes within approximately 3 µg/day are acceptable
- Sex steroids: patients on sex steroids must have been taking them of at least 2 months at screening; dose changes within approximately 25% of the screening dose are acceptable as are changes within class (e.g., from one oral contraceptive to another, or from one selective estrogen receptor to another).

The following medications are **NOT** allowed for Phase 2b or Phase 3:

- Weight loss agents and medications taken to affect appetite (e.g. Orlistat®, Lorcaserin, Qsymia®, Contrave®/Mysimba®, GLP-1 analogs as well as any over-the counter medication and herbal agent).

In the interest of patients' safety and acceptable standards of medical care, the investigator will be permitted to prescribe treatments. All prescribed treatments should be maintained at constant dose if possible and must be recorded in the patient' eCRFs.

6.6 Rescue Medicine

This section is not applicable.

7 STUDY DRUG DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study or the Principal Investigator (PI) in accordance with the Sponsor may terminate a participant from the study.

7.1 Discontinuation of Study Treatment

Patients (or legally authorized representatives) can decline to continue receiving the study drug and/or other protocol-required procedures at any time during the study.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

7.2 Participant Discontinuation/Withdrawal from the Study

Patients have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or institution.

Reasons for removal from protocol-required treatment or procedures might include the following:

- Study withdrawal: Participants are free to withdraw from participation in the study at any time upon request.
    - For the Netherlands, if patients show resistance (refuse to cooperate) during the study, the investigator will follow the guidelines listed below and will have to stop the study immediately:
        - Code of Conduct relating to expressions of abjection by minors participating in medical research;
        - Code of conduct relating to the expression of objection by people with mental disabilities in the context of the Medical Research in Human Subjects Act (WMO);
- Pregnancy: Withdraw the patient from the clinical trial and follow the procedure described in Section 8.1.2.2;

- Adverse Events: Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant. Complete an Adverse Event Form;
- Eligibility: The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation;
- Protocol violation: Lack of compliance to protocol requirements and/or procedures;
- Lost to follow-up: Refer to Section 7.3;
- Death;
- Other: This category is to be used for a patient who discontinues due to a reason other than those specified in the predefined categories above (e.g. including but not limited to administrative deviations that preclude satisfactory completion of protocol assessments).

The eCRF will be completed following instructions provided to the site.

Any patient who discontinues early from the study should be strongly encouraged to come back to the study site to conduct all study assessment described under Early Termination Visit in the Schedule of Assessments. Minimum assessments include HQ-CT administration, safety assessments, Caregiver Global Impression of Severity - Hyperphagia (CgGIS-H) and Clinical Global Impression of Severity - Hyperphagia (CGIS-H).

7.2.1 Handling of Participant Withdrawal or Termination

Before interrupting or discontinuing study drug, the investigator should contact the Sponsor or designee (except in the case of an emergency) in order to discuss the proposed reason. It has to be documented whether or not each patient completes the study. If any patient study treatment or observations are discontinued, the reason must be recorded in the patient medical file and in the eCRF. Patients will be instructed by the investigator to immediately contact their personal primary care physician to resume to their entire PWS treatment.

The investigator is to discuss with the patient appropriate processes for discontinuation and the options for procedures that may continue such as collection of data, including endpoints and AEs.

The investigator must document the agreement in the procedures that the patient will continue with and the level of follow-up that is agreed to by the patient (e.g. in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records.).

If a patient withdraws due to an AE at any time during the study, the investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

7.2.2 Replacement of Patients

Patients who withdraw from the study after randomization will not be replaced.

For Phase 2b, the total number of randomized patients 8 to 65 years of age is estimated to be approximately 50 patients per group.

For Phase 3, the total number of randomized patients is estimated to be approximately 50 patients per group but will be determined following analysis of data at the completion of the Phase 2b Core Period.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file as instructed by the Sponsor/representative;
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the Institutional Review Board (IRB)/Ethics Committee (EC) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance with protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB/EC, and/or Regulatory Authorities.

8 STUDY ASSESSMENTS, PROCEDURES AND SCHEDULE

8.1 Study Procedures/Evaluations

8.1.1 Study Specific Procedures

The following is a list of study specific procedures (i.e. not part of Standard Clinical Care) and their description:

- **Dual energy X-ray absorptiometry (DXA) scan:** Pertinent variables of body composition, including total body fat mass, lean body mass, and bone mineral density will be measured by DXA. Also see Section 9.1.2 and Section 10.1.5;
- **ECG (12-lead):** Also see Section 10.1.6;
- **PK:** Blood samples for PK analysis must be drawn per the Schedule of Activities tables available in Section 1.2. A Manual detailing the PK sample collection, preparation, storage and shipping process will be provided. Also see Section 8.1.2.3.1;
- **HQ-CT, CgGIS-H/CGIS-H, Caregiver Global Impression of Change - Hyperphagia (CgGIC-H)/Clinical Global Impression of Change – Hyperphagia (CGIC-H), Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Appetite-NRS, Pediatric Quality of Life inventory™ (PedsQL™) Parent-Proxy age-appropriate Report, Developmental Behavior Checklist 2-Parent/Carer version (DBC2-P) Questionnaires, Zarit Burden Interview (ZBI), and European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L) Self-complete version and Proxy version 1:** Administration guidelines for these questionnaires will be provided. Also see Section 11.2, Section 11.3, Section 11.4 and Section 11.5.

  Caregivers will receive instructions on questionnaires completion and will complete the assessment on site throughout the clinical trial.

  Questionnaires completed by the investigator: each questionnaire should be completed by the same investigator for a given patient if possible. If this is not possible, an overlapping assessment should be performed between the previous and the new investigator;
- **Intelligence Quotient (IQ) testing:** IQ test scores and dates of completion will be collected if available in the patient's medical records;
- **Clinical Laboratory Testing:** All laboratory evaluations are described in Section 8.1.2 below.

8.1.2 Laboratory Procedures/Evaluations

8.1.2.1 Clinical Laboratory Evaluations

Patients will be required to fast for approximately 8 hours before visits requiring fasted blood sampling.

All clinical laboratory assays (except urine pregnancy test) will be performed at central laboratories according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Abnormal laboratory values which are unexpected or not explained by the clinical condition should be repeated until confirmed, explained, or resolved.

The investigator will be copied on all laboratory reports and will review and assess all out of range results to evaluate clinical significance. Any abnormal laboratory values, assessed as clinically significant on blood samples performed at screening, will be recorded in the medical history. Any abnormal laboratory value changes (safety laboratory evaluations) starting from the time of signing the ICF assessed as clinically significant will be recorded as an AE as appropriate (refer to Section 10.3).

Clinical laboratory evaluations will include:

- Safety laboratory evaluations in fasting condition (fasting for approximately 8 hours) as summarized in Table 5;
- Blood glucose and insulin (fasting for approximately 8 hours and postprandial during the Core Period/fasting for approximately 8 hours only during the Extension Period);
- Plasma ghrelin (AG and UAG) (fasting for approximately 8 hours and postprandial during the Core Period/fasting for approximately 8 hours only during the Extension Period);
- $HbA1_C$;
- Anti-livoletide antibodies (anti-drug antibodies [ADA]). Any patient who tests positive for ADA will be followed until the serum titers revert to baseline;
- Insulin-like growth factor-1 (IGF-1);
- Follicle stimulating hormone (FSH)/luteinizing hormone (LH) when needed.

Dipsticks for pregnancy test will be provided.

See also Section 10.1.7.

Clinical chemistry:	
Sodium	Albumin
Potassium	Uric acid
Calcium	Lactate dehydrogenase (LDH)
Chloride	Alanine aminotransferase (ALT)
Bicarbonate	Alkaline phosphatase (ALP)
Urea nitrogen	Total cholesterol
Creatinine	Triglycerides
Glucose	Low density lipoprotein (LDL)
Total bilirubin	High density lipoprotein (HDL)
Total protein	
Aspartate aminotransferase (AST)	
Coagulation:	
Prothrombin time	
Activated partial thromboplastin time	
Hematology:	
Hemoglobin	Platelets
Hematocrit	White blood cell count (including differentials)
Red blood cell count	
Urinalysis:	
pH	Specific gravity
Protein	Leukocyte esterase
Glucose	Blood (free hemoglobin)
Ketones	Nitrite
Bilirubin	Urobilinogen

Table 5: Summary table of clinical laboratory parameters assessed during the study.

In the Phase 2b study Core and Extension Periods, the estimated blood volume taken from patients will be approximately 145 ml for patients 4 to 7 years of age and approximately 189 mL for patients 8-65 years of age. This volume does not include any blood samples that would be

needed for retest. For patients 4-15 years of age, the scheduled blood volumes to be drawn for the study are <2.5% of estimated total blood volume per single draw and <5% of estimated total blood volume per 30-day period as per pediatric guidelines.

In the Phase 3 study Core and Extension Periods, the estimated blood volume taken from patients will be approximately 184 mL. This volume does not include any blood samples that would be needed for retest. For patients 8-15 years of age, the scheduled blood volumes to be drawn for the study are <2.5% of estimated total blood volume per single draw and <5% of estimated total blood volume per 30-day period as per pediatric guidelines.

8.1.2.2 Pregnancy

8.1.2.2.1 Definition of Childbearing Potential: Female Patients

A female patient is considered of childbearing potential if she:

- Is anatomically and physiologically capable of becoming pregnant; and
- Will be or could possibly be sexually active with a male while undergoing study treatment with the possibility of posing harm to a fetus.

A female patient is considered to be of non-childbearing potential (i.e. physiologically incapable of becoming pregnant) if she:

- Is prepubertal or pre-menarchal; or
- Is post-menopausal (at least 12 months consecutively amenorrhoeic, at least 45 years of age, and has a LH and FSH levels in the local post-menopausal ranges); or
- Is surgically sterilized (i.e. bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) with surgery at least 1 month before the first dose of study treatment; or
- Has a documented congenital or acquired disorder that is incompatible with pregnancy.

8.1.2.2.2 Definition of Childbearing Potential: Male Patients

A male patient is considered of childbearing potential if he:

- Is anatomically and physiologically capable of causing a pregnancy in a female partner; and
- Will be or could possibly be sexually active with a female (who is or may become pregnant) while undergoing study treatment with the possibility of posing harm to a fetus.

A male patient is considered to be of non-childbearing potential if he:

- Is prepubertal or pre-spermarchal; or
- Has a documented successful vasectomy (with confirmed azoospermia).

8.1.2.2.3 Pregnancy Testing

All female patients of childbearing potential must have a negative pregnancy test (urine) at all visits when the test is performed.

Pregnancy tests will be performed for WCBP only. A urine pregnancy test will be performed at screening, or after the onset of menarche if the patient was pre-menarchal at screening, and urine

pregnancy tests will be performed thereafter at each study visit and any time pregnancy is suspected.

Positive urine tests performed using dipsticks at the study site are to be confirmed by serum testing. Serum testing will be performed at a central laboratory.

The results of the pregnancy test must be known before study drug administration.

8.1.2.2.4 Reporting

Pregnancy is rarely observed in PWS. If a patient becomes pregnant during the study treatment period or within 14 days after the last dose of study drug the Sponsor or designee must be notified. If the pregnancy occurs during the treatment period, the study drug will be discontinued, and Early Termination study procedures will be performed.

A pregnancy must be reported by the investigator to the Sponsor or designee within 24 hours of awareness. Pregnancies must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the investigator/site the Exposure In Utero (EIU) form for completion. The investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

The pregnancy should be followed by the investigator until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., congenital anomaly), the investigator should follow the procedures for reporting an SAE.

8.1.2.3 Other Assays or Procedures

8.1.2.3.1 Pharmacokinetics

During the Core period, all patients will have blood samples collected at three timepoints at Visit 3 (Week 5/Day 29). During the Extension period, a subset of patients (Up to N=20/livoletide group; 40 patients in total) at selected study sites will undergo PK profile sampling at Visit 6 (Week 18/Day 120). In patients from whom profile samples are not collected (i.e. sparse sampling), three samples will be collected. At Visit 7 (Week 27/Day 183) an additional set of sparse samples will be collected from all patients. All timepoints are detailed in the Pharmacokinetic Schedule of Activities Section 1.2.3.

For all samples, the date as well as the nominal and actual time of each sample collection will be recorded on the medical record and then reported in the eCRF, together with the time of the study drug injection at the same visit.

Whole blood will be collected in tubes of up to 3 mL containing spray-dried K3 ethylenediaminetetraacetic acid as anti-coagulant for the analysis of livoletide. Additional details will be provided in a separate manual.

8.1.2.4 Specimen Preparation, Handling and Storage and Shipment

A Manual detailing the sample collection, preparation, handling, storage, and shipping process for PK and safety evaluations and other laboratory assessments will be provided prior to site initiation.

8.2 Study Schedule

All required study procedures are outlined in the Schedule of Activities tables available in Section 1.2. All information required by the protocol must be recorded.

As indicated in the Schedule of Activities tables, a window of ±3 days for visits during the double-blind treatment period and ±7 days for visits during the Extension Period (except Visit 6 for Phase 2b, which has a window of ±4 days) is allowable for study procedures, as long as the proper order of procedures and assessments, as described in the sections below, is maintained. These windows are not applicable during the baseline period and other periods for which specific time limits have been defined and cannot be exceeded (e.g. screening period: Day -28 to -1).

Patients will be required to fast for approximately 8 hours before visits requiring blood sampling.

During the Core Period, patients will be required to consume an isocaloric breakfast prepared at the study center at visits when samples are taken for insulin and glucose profiles, AG and UAG profiles and when the appetite-NRS is administered.

8.2.1 Phase 2b Study Schedule

8.2.1.1 Phase 2b Visit 1: Screening and Enrollment (Week -4 to -1/Day -28 to -1)

The following procedures will be performed during the screening visit:

- Obtain signed informed consent and assent from potential patients and/or parents or legal guardians, as appropriate;
- Assign a study specific patient number;
- Contact the IRT to register the patient in the study;
- Obtain demographics, medical and disease history, prior and concomitant medications (Note: Tanner staging will be included as part of the medical history if performed in the past 2 months. Patient will be staged if staging not available);
- Assess inclusion and exclusion criteria to determine eligibility;
- Collect IQ test scores and dates of completion if available in the patient's medical record;
- Perform a 12-lead ECG;
- Perform medical examinations (complete physical examination, vital signs);
- Obtain height, WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition (after fasting for approximately 8 hours);
- Collect blood sample for HbA1c analysis;
- Review/record of AEs that occurred since the signature of the ICF. For AEs classification, refer to Section 10.4;
- Review and completion of questionnaires on electronic device (eDevice) on site and ensure all questionnaires have been completed before the patient leaves the site:

- For patients 8 to 65 years of age, administer appetite-NRS to patients for training and acclimation purposes;
- Administer HQ-CT to primary caregiver.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws

8.2.1.2 Phase 2b Visit 2: Randomization (Week 1/Day 1)

The randomization visit will occur a minimum of 2 weeks after the screening visit.

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following procedures will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Contact the IRT to randomize the patient and obtain study drug assignment.

In addition, the following activities will be performed for baseline evaluations:

- For patients 8 to 65 years of age, perform 12-lead ECG before administering study drug and 1 hour post-dose;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 2);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- For patients 8 to 65 years of age, collect blood samples at selected time points for the following analyses:
  - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
  - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- For patients 4 to 7 years of age, collect blood samples for glucose, insulin, AG and UAG (fasting)
- Collect blood samples for the following analyses:
  - HbA1c;
  - IGF-1;
  - ADA;
- For patients 8 to 65 years of age, isocaloric breakfast taken on site and record any food not consumed;

- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - For patients 8 to 65 years of age, administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
    - Administer HQ-CT to primary caregiver;
    - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
    - Administer CgGIS-H to primary caregiver;
    - Investigator to complete CGIS-H and CGI-S;
    - Administer ZBI to primary caregiver;
    - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
    - Administer DBC2-P questionnaire to primary caregiver;
- Dispense glucometer kit to the patients with T2D if needed (i.e. if they do not have one);
- Dispense study drug and supplies for treatment until next visit;
- For patients 8 to 65 years of age, administer first dose of the study drug after the last sample has been taken for the glucose, insulin, AG, and UAG profiles;
- For patients 4 to 7 years of age, administer first dose of the study drug after all the patient assessments were completed;
- Ask and remind caregiver to administer study drug daily and at approximately the same time before breakfast.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.1.3 Phase 2b Visit 3: Core Period (Week 5/Day 29)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/Record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;

- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- For patients 8 to 65 years of age, collect blood samples at selected time points for the following analyses:
    - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
    - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- For patients 4 to 7 years of age, collect blood samples for glucose, insulin, AG and UAG (fasting)
- Collect blood sample for ADA;
- Collect blood samples for PK (3-timepoint sampling: before, 30 minutes and 180 minutes post-start of breakfast)
- Isocaloric breakfast taken on site and record any food not consumed;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - For patients 8 to 65 years of age, administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignment and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug 30 minutes before starting breakfast;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.1.4 Phase 2b Visit 4: Core Period (Week 9/Day 57)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;

- Review/Record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer HQ-CT to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact the IRT to obtain study drug assignment and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.1.5 Phase 2b Visit 5: End of Core Period/Core Period Early Treatment Discontinuation and Primary Endpoint Evaluation (Week 13/Day 85)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- For patients 8 to 65 years of age, perform 12-lead ECG before administering study drug and 1 hour post-dose;
- For patient 4 to 7 years of age, perform 12-lead ECG only before administering the study drug;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 5);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- For patients 8 to 65 years of age, collect blood samples at selected time points for the following analyses:

  - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
  - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- For patients 4 to 7 years, collect blood samples for glucose, insulin, AG and UAG (fasting)
- Collect blood samples for the following analyses:
  - HbA1c;
  - IGF-1;
  - ADA;
- For patients 8 to 65 years of age, isocaloric breakfast taken on site and record any food not consumed;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - For patients 8 to 65 years of age, administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
  - Administer HQ-CT to primary caregiver;
  - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
  - Administer ZBI to primary caregiver;
  - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
  - Administer DBC2-P questionnaire to primary caregiver;
- Administer last dose of the Core Period 30 minutes before starting breakfast;
- Check drug accountability and compliance, collect all returned study drug;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check patient BW and adjust dose volume accordingly for the extension phase;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws.

8.2.1.6 Phase 2b Visit 6: Extension Period (Week 18/Day 120)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Collect blood samples for PK (either profile or sparse sampling);
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.1.7 Phase 2b Visit 7: Extension Period (Week 27/Day 183)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- For patients 8 to 65 years of age, perform a 12-lead ECG before administering study drug and 1 hour post-dose;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 7);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;

- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples for the following analyses:
  - HbA1c;
  - Fasting glucose and insulin;
  - Fasting AG and UAG;
  - IGF-1;
  - ADA;
- Collect blood samples for PK (sparse sampling)
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer HQ-CT to primary caregiver;
  - Administer age-appropriate PedsQL^{TM} Parent Proxy-Report to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
  - Administer ZBI to primary caregiver;
  - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
  - Administer DBC2-P questionnaire to primary caregiver;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws.

8.2.1.8 Phase 2b Visit 8: Extension Period (Week 40/Day 274)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;

- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples for the following analyses:
  - HbA1c;
  - Fasting glucose and insulin;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer HQ-CT to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.1.9 Phase 2b Visit 9: End of Extension Period/Extension Period Early Treatment Discontinuation (Week 53/Day 365)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- For patients 8 to 65 years of age, perform a 12-lead ECG before administering study drug and 1 hour post dose;
- For patients 4 to 7 years of age, perform 12-lead ECG only before administering study drug;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients <18 years of age only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 9);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;

- Collect blood samples for the following analyses:
  - HbA1c;
  - Fasting glucose and insulin;
  - Fasting AG and UAG;
  - IGF-1;
  - ADA;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer HQ-CT to primary caregiver;
  - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
  - Administer ZBI to primary caregiver;
  - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
  - Administer DBC2-P questionnaire to primary caregiver;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws.

8.2.1.10 Phase 2b Visit 10: End of Study Telephone Follow-up (Week 57/Day 393)

Patients will be contacted by telephone to collect information about AEs and concomitant medications related to AEs.

8.2.2 Phase 3 Study Schedule

8.2.2.1 Phase 3 Visit 1: Screening and Enrollment (Week -4 to -1/Day -28 to -1)

The following procedures will be performed during the screening visit:

- Obtain signed informed consent and assent from potential patients and/or parents or legal guardians, as appropriate;
- Assign a study specific patient number;
- Contact the IRT to register the patient in the study;
- Obtain demographics, medical and disease history, prior and concomitant medications (Note: Tanner staging will be included as part of the medical history if performed in the past 2 months. Patient will be staged if staging not available);
- Assess inclusion and exclusion criteria to determine eligibility;

- Collect IQ test scores and dates of completion if available in the patient's medical record;
- Perform a 12-lead ECG;
- Perform medical examinations (complete physical examination, vital signs);
- Obtain height, WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood sample for HbA1c analysis;
- Review/record of AEs that occurred since the signature of the ICF. For AEs classification, refer to Section 10.4;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer appetite-NRS to patients for training and acclimation purposes;
    - Administer HQ-CT to primary caregiver.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws, considering the blood draws to be done in fasting conditions.

8.2.2.2 Phase 3 Visit 2: Randomization (Week 1/Day 1)

The randomization visit will occur a minimum of 2 weeks after the screening visit.

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following procedures will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Contact the IRT to randomize the patient and obtain study drug assignment.

In addition, the following activities will be performed for baseline evaluations:

- Perform 12-lead ECG before administering study drug and 1 hour post-dose;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 2);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples at selected time points for the following analyses:

  - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
  - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- Collect blood samples for the following analyses:
  - HbA1c;
  - IGF-1;
  - ADA;
- Isocaloric breakfast taken on site and record any food not consumed;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
  - Administer HQ-CT to primary caregiver;
  - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
  - Administer CgGIS-H to primary caregiver;
  - Investigator to complete CGIS-H and CGI-S;
  - Administer ZBI to primary caregiver;
  - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
  - Administer DBC2-P questionnaire to primary caregiver;
- Dispense glucometer kit to the patients with T2D if needed (i.e. if they do not have one);
- Dispense study drug and supplies for treatment until next visit;
- Administer first dose of the study drug after the last sample has been taken for the glucose, insulin, AG, and AUG profiles;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws, considering the blood draws to be done in fasting conditions.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.2.3 Phase 3 Visit 3: Core Period (Week 5/Day 29)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/Record of AEs that occurred since the last visit on site;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples at selected time points for the following analyses:
    - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
    - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- Isocaloric breakfast taken on site and record any food not consumed;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignments and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug 30 minutes before starting breakfast;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.2.4 Phase 3 Visit 4: Core Period (Week 9/Day 57)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/Record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact the IRT to obtain study drug assignment and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.2.5 Phase 3 Visit 5: Core Period (Week 13/Day 85)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 5);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples at selected time points for the following analyses:
    - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
    - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- Collect blood samples for the following analyses:

  - HbA1c;
  - IGF-1;
  - ADA;
- Isocaloric breakfast taken on site and record any food not consumed;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
  - Administer HQ-CT to primary caregiver;
  - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
  - Administer ZBI to primary caregiver;
  - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
  - Administer DBC2-P questionnaire to primary caregiver;
- Contact IRT for study drug assignment and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug 30 minutes before starting breakfast;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.2.6 Phase 3 Visit 6: Core Period (Week 18/Day 120)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;

- Perform safety laboratory evaluations in fasting condition;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
  - Administer HQ-CT to primary caregiver;
  - Administer CgGIS-H and CgGIC-H to primary caregiver;
  - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignment and dispense study drug and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer study drug;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.2.7 Phase 3 Visit 7: End of Core Period/Core Period Early Discontinuation (Week 27/Day 183)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform a 12-lead ECG;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 7);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples at selected time points for the following analyses:
  - Glucose and insulin profiles (before, 30 minutes and 180 minutes post-start of breakfast);
  - AG and UAG profiles (before, 30 minutes and 180 minutes post-start of breakfast);
- Collect blood samples for the following analyses:
  - HbA1c;
  - IGF-1;
  - ADA;
- Isocaloric breakfast taken on site and record any food not consumed;

- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer appetite-NRS to patients, under the supervision of the study personnel, at selected time points (before, at the end, and 120 minutes post-start of breakfast);
    - Administer HQ-CT to primary caregiver;
    - Administer age-appropriate PedsQL™ Parent Proxy-Report to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
    - Administer ZBI to primary caregiver;
    - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
    - Administer DBC2-P questionnaire to primary caregiver;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Check patient BW and adjust dose volume accordingly for the extension phase;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws, considering the blood draws to be done in fasting conditions.

Note: An isocaloric breakfast will be administered at this visit. Any food not consumed should be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes. The NRS should be administered before any blood sampling and study drug administration in order for patients to complete the questionnaire while they are relaxed.

8.2.2.8 Phase 3 Visit 8: Extension Period (Week 30/Day 211)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform medical examinations (abbreviated physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;

- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

8.2.2.9 Phase 3 Visit 9: Extension Period (Week 40/Day 274)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform a 12-lead ECG;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 9);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Collect blood sample for Hb1Ac analysis;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer HQ-CT to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
- Contact IRT for study drug assignment and dispense livoletide and supplies for treatment until next visit;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide;
- Ask and remind caregiver to administer study drug daily and at approximately at the same time before breakfast.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws, considering the blood draws to be done in fasting conditions.

8.2.2.10 Phase 3 Visit 10: End of Extension Period/Extension Period Early Treatment Discontinuation (Week 53/Day 365)

The patient should have been fasting for approximately 8 hours when they attend this visit.

The following activities will be performed:

- Review of concomitant medications;
- Review/record of AEs that occurred since the last visit on site;
- Perform a 12-lead ECG;
- Perform medical examinations (complete physical examination, vital signs);
- Record height (patients aged <18 years only), WC, BW, and BMI before breakfast;
- Perform a DXA scan (can be obtained within 2 weeks prior to Visit 10);
- Perform a urine pregnancy test (WCBP only). A positive urine pregnancy test should be confirmed with a serum sample;
- Perform safety laboratory evaluations in fasting condition;
- Collect blood samples for the following analyses:
    - HbA1c;
    - Fasting insulin ;
    - Fasting AG and UAG ;
    - IGF-1;
    - ADA;
- Review and completion of questionnaires on eDevice on site and ensure all questionnaires have been completed before the patient leaves the site:
    - Administer HQ-CT to primary caregiver;
    - Administer age-appropriate PedsQL^{TM} Parent Proxy-Report to primary caregiver;
    - Administer CgGIS-H and CgGIC-H to primary caregiver;
    - Investigator to complete CGIS-H, CGIC-H, CGI-I, and CGI-S;
    - Administer ZBI to primary caregiver;
    - Administer EQ-5D-5L Self-complete version and Proxy version 1 to the primary caregiver;
    - Administer DBC2-P questionnaire to primary caregiver;
- Check drug accountability and compliance, collect all returned study drug;
- Administer livoletide.

Note: Whenever the 12-lead ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws, considering the blood draws to be done in fasting conditions.

8.2.2.11 hase 3 Visit 11: End of Study Telephone Follow-up (Week 57/Day 393)

Patients will be contacted by telephone to collect information about AEs and concomitant medications related to AEs.

8.2.3 Early Termination Visit

For those patients who terminate the study early, every effort will be made to determine their reason for dropping out, and to complete the Early Treatment Discontinuation Visit assessments described in Section 7.2.1 and in the Schedule of Activities tables available in Section 1.2.

For details of the Early Treatment Discontinuation Visit activities to be performed, please refer to the following sections:

- Phase 2b Core Period, Section 8.2.1.5;
- Phase 2b Extension Period, Section 8.2.1.9;
- Phase 3 Core Period, Section 8.2.2.7;
- Phase 3 Extension Period, Section 8.2.2.10.

8.2.4 Schedule of Activities Tables

Please refer to the following sections for the Schedule of Activities tables:

- Phase 2b Core Period, Section 1.2.1;
- Phase 2b Extension Period, Section 1.2.2;
- Phase 3 Core Period, Section 1.2.4;
- Phase 3 Extension Period, Section 1.2.5.

9 ASSESSMENT OF EFFICACY

9.1 Specifications of Primary and Secondary Efficacy Parameters

Phase 2b

Efficacy assessments in the Phase 2b Core Period will include the following:

- HQ-CT (primary endpoint): Change from baseline to the end of the 3-month Core Period in food-related behaviors, as assessed by the HQ-CT total score (see Section 19.2 Appendix B for HQ-CT content);
- Total body fat mass, WC, and BW: Change from baseline to the end of the 3-month Core Period.

Efficacy assessments in the Phase 2b Extension Period will include the following:

- HQ-CT: Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period in

food-related behaviors, as assessed by the HQ-CT total score (see Section 19.2 Appendix B for HQ-CT content);

- Total body fat mass, WC, and BW: Change from baseline to the end of the 9-month Extension Period and change from the end of the 3-month Core Period to the end of the 9-month Extension Period.

Phase 3

Efficacy assessments in the Phase 3 Core Period will include the following:

- HQ-CT (primary endpoint): Change from baseline to the end of the 6-month Core Period in food-related behaviors, as assessed by the HQ-CT total score (see Section 19.2 Appendix B for HQ-CT content);
- Total body fat mass, WC, and BW: Change from baseline to the end of the 6-month Core Period.

Efficacy assessments in the Phase 3 Extension Period will include the following:

- HQ-CT: Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period in food-related behaviors, as assessed by the HQ-CT total score (see Section 19.2 Appendix B for HQ-CT content);
- Total body fat mass, WC, and BW: Change from baseline to the end of the 6-month Extension Period and change from the end of the 6-month Core Period to the end of the 6-month Extension Period.

9.1.1 Hyperphagia Questionnaire for Clinical Trials

Food-related behavior will be assessed through the HQ-CT questionnaire, a validated 9-item caregiver-reported outcomes measure. HQ-CT (and other study questionnaires) will be provided on eDevice.

In order to optimize the consistency with which the HQ-CT will be administered and to maximize data accuracy across sites and studies, sites will be provided with administration guidelines upon study initiation.

9.1.2 Total Body Fat Mass

Total body fat mass will be assessed by DXA.

Dual energy X-ray absorptiometry enables quantification of fat, lean, and bone tissues. The two low-energy levels used in DXA and their differential attenuation through the body allow the discrimination of total body adipose and soft tissue, in addition to bone mineral content and bone mineral density. Dual energy X-ray absorptiometry is fast and user-friendly for the patient and the operator. A typical whole-body scan takes approximately 10 to 20 minutes and exposes the patient to low levels of radiation.

DXAs will be conducted at each local facility using standardized procedures and settings. DXA images will be read by an independent central reader, blinded to the patient's treatment assignment:

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Only GE Healthcare or Hologic systems capable of measuring total body composition will be used in this study and must be approved by the core laboratory.

Specific acquisition guidelines will be provided in a separate DXA Acquisition Manual.

Patients will be scanned in light clothing, in supine position, and the entire body will be scanned from the top of the head down to the feet in a rectilinear manner. Measurements should be made for four different regions (head, arms, trunk, and legs) and for the body as a whole.

9.1.3 Waist Circumference

The WC should be measured before breakfast at the superior border of iliac crest, according to recommendations from the Anthropometry Procedures Manual of the National Health and Nutrition Examination Survey, Revised 2007. A separate document describing the procedure will be provided to sites.

9.1.4 Body Weight

Before breakfast, patients will be weighed clothed (underwear, light gown or light clothing), without footwear (shoes or sandals) or heavy jewelry, using a calibrated scale. The same scale should be used throughout the study if possible. The conditions under which patients are weighed should be kept consistent if possible.

10 ASSESSMENT OF SAFETY

10.1 Specification of Safety Parameters

Please refer to Schedules of Activities in Section 1.2.

10.1.1 Adverse Events

All AEs must be collected beginning from the time the patient signs the ICF until the last study visit or 30 days (by phone only) after the last dose of study drug, whichever is longer. Please refer to Section 10.3, Section 10.4, and Section 10.5 for the detailed definition of AEs and reporting procedures.

10.1.2 Vital Signs

Vital signs include respiration rate, pulse rate, and blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), measured sitting after the patient has rested comfortably for

5 minutes. Each patient's blood pressure should be taken using the same arm. Temperature will be recorded in Celsius or Fahrenheit. Pulse rate will be counted for a full minute and recorded in beats per minute. Respirations will be counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital signs may be obtained at the discretion of the investigator.

10.1.3 Height and Body Mass Index

Height will be measured before breakfast, with a wall-mounted or portable stadiometer, to the nearest 0.1 cm and without shoes. Height will be measured for adults once at screening, and at each visit for patients <18 years of age.

Body mass index will be calculated at each visit.

10.1.4 Physical Examination

A complete or abbreviated physical examination will be obtained at selected visits. At any time, targeted physical examination may be performed if needed based on AEs and positives from review of systems.

The examination of the following will be performed for a complete physical examination: heart, peripheral vasculature, lungs, musculoskeletal system, abdomen, neurologic function, endocrine system, genito-urinary system, skin, lymph nodes, and any areas pertinent to any AEs and positives from review of systems.

The following systems will be examined for an abbreviated physical examination: heart, lungs, abdomen, and any areas pertinent to any AEs and positives from review of systems.

Significant findings that are observed at screening must be recorded as Medical History. Clinically significant changes from the screening visit which meet the definition of an AE must be recorded as an AE.

10.1.5 Lean Body Mass and Bone Mineral Density

Lean body mass and bone mineral density will be assessed by DXA as described in Section 9.1.2.

10.1.6 Electrocardiograms

For patients 8 to 65 years of age, ECG will be performed in triplicate pre-dose and 1 hour post dose (except at the screening visit). For patients 4 to 7 years of age, ECG will be performed in triplicate pre-dose only, at screening visit, end of Core Period visit and end of study visit.

Twelve-lead digital ECGs will be obtained after 10 minutes in a supine position. Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, it is preferred that the assessments occur in the following order: 12-lead ECG, vital signs, and blood draws.

Skin preparation should be thorough and electrodes should be placed according to standard 12-lead ECG placement.

ECGs will be digitally recorded and printed on paper. The printed paper ECGs will be used for "real time" bedside ECG assessment by the investigator (or designee) who will be responsible for the overall interpretation and determination of the clinical significance of any potential ECG findings. Digital ECGs will be submitted to the ECG core laboratory, which will perform the

digital ECG analysis and interpretation in this study using standard methodology. If the central reader identifies an abnormality, per the study alert criteria, the investigator will be notified who will review the ECG and report any AEs as necessary.

The following variables will be reported: HR, RR interval, PR interval, QRS complex duration, QT interval, QTcB, and QT interval corrected for HR by Fridericia's formula (QTcF). The investigator may add additional 12-lead ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason.

Sites will be provided with ECG machines.

Instruction for ECG acquisition will be provided in a separate manual. ECG recordings will be read by an independent central reader, blinded to the patient's treatment assignment:

Emily Lay, MS

Project Manager

Medpace Core Laboratories

5375 Medpace Way

Cincinnati, Ohio 45227

Tel: +1.513.579.9911, ext. 12626

Fax: +1.513.579.0444

E-mail: e.lay@medpace.com

10.1.7 Safety Laboratory Parameters

Safety laboratory parameters include safety laboratory evaluations (clinical chemistry including lipids, coagulation, hematology, and urinalysis) described in Section 8.1.2 (Table 5), as well as HbA1c, ghrelin, ADA, and IGF-1.

Any patient that tests positive for ADA will be followed until the serum titers revert to baseline.

Details on sample collection, processing, and shipping will be provided in a Laboratory Manual.

All samples will be shipped to a central laboratory:

Europe

Tatiana Afrikanova, PhD

Project Manager

Medpace Reference Laboratories

Technologielaan 19

3001 Leuven, Belgium

Tel: +32 16 40 77 75 ext. 23626

E-mail: t.afrikanova@medpacelab.com

United States

Dana Lee

Project Manager

Medpace Reference Laboratories

5365 Medpace Way

Cincinnati, Ohio 45227

Tel: +1.513.366.3270, ext. 11279

Mobile: +1.513.760.2060

Fax: +1.513.366.3273

E-mail: d.lee1@medpacelab.com

10.2 Safety Measures for the Management of Hypoglycemia

The clinical sites in this study are expected to be experienced in the management of diabetes mellitus, including common complications such as hypoglycemia. At the clinical site, in case of symptomatic hypoglycemia, sugar, glucose drinks, or other sources of carbohydrates appropriate for the treatment of hypoglycemia will be available. If there is no adequate response to oral treatment or the patient is unable to eat or drink, intravenous dextrose and intramuscular glucagon will also be available.

Patients with T2D, as well as their caregiver (as applicable), will be instructed to monitor fasting glucose levels (according to their usual practice) during the treatment periods using a glucometer. In addition, patients and their caregiver (as applicable) will be educated to recognize symptoms of hypoglycemia and will be instructed to take or give sugar if fasting glucose value is below 70 mg/dL (3.9 mmol/L) and to repeat glucose check in the next 30 minutes and the next hour. They will be instructed to call the study center if one of the repeat values is below 70 mg/dL (3.9 mmol/L) for further investigation and management.

10.3 Adverse Events and Serious Adverse Events

10.3.1 Definition of Adverse Events, Adverse Drug Reactions, and Unexpected Adverse Drug Reactions

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

- All AEs, regardless of relationship to study drug, should be collected beginning from the time the patient signs the ICF until the last study visit or 30 days after the last dose of study drug, whichever is later. (Any SAE judged by the investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.) Adverse events in study subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes;
- Wherever possible, a specific disease or syndrome, rather than individual associated signs and symptoms, should be identified by the investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease

or syndrome by the investigator, it should be recorded as a separate AE. Additionally, the condition that led to a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure. Any medical condition already present at screening should not be reported as an AE unless the medical condition or signs or symptoms present at baseline worsens in severity or seriousness at any time during the study. Clinically significant examination (e.g. ECG) findings that are detected during the study or are present at screening and worsen during the study should be reported as an AE.

  - An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not. It is up to the investigator to determine whether an abnormal laboratory value constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g. if new onset viral hepatitis is causing elevated ALT, the specific hepatitis and not the elevated ALT should be listed as the AE);
  - Examples of laboratory abnormalities that should be considered AEs include those that result in withdrawal of the study treatment or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be recorded on the appropriate AE page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all safety laboratory findings in all patients. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE;

- Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to study drug;
- Patients who develop toxicity on study will be followed until the event resolves, stabilizes, or returns to baseline.

Adverse Reaction: All noxious and unintended responses to study drug at any dose should be considered to be adverse reactions. "Responses to study drug" means that there is a causal relationship between the study drug and the responses. "*Suspected* adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

Unexpected Adverse Reaction: An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For the study drug, the reference safety information (RSI) is included in the version of the livoletide IB currently in force.

10.3.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which, in view of either the investigator or Sponsor, the patient was at

immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.);

- Requires inpatient hospitalization or prolongation of an existing hospitalization

  Notes:

  Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalizations that occur during elective surgery should be recorded as AEs and assessed for seriousness.

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

  - Hospitalizations for respite/hospice care;
  - Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration);

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect; or
- Is determined to be an important medical event (at the discretion of the Investigator).

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4 Classification of an Adverse Event

10.4.1 Severity of Event

The assessment of severity must be provided by the investigator and based on the investigator's clinical judgment. Maximum severity should be assigned to one of the following categories:

- Mild: An AE that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities;
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities;
- Severe: An AE that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Refer to Section 10.3.2 for the definition of an SAE.

10.4.2 Relationship to Study Drug

The investigator will categorize each AE as to its potential relationship to study drug: **unrelated**, **unlikely related**, **possibly related**, **probably related,** and **definitely related**. Items to be considered when assessing the relationship of an AE to the study treatment are as follows:

- Temporal relationship of the onset of the event to the initiation of the study treatment;
- The course of the event, considering 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 patient known to increase the occurrence of the event;
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

The relationship categories of unrelated and unlikely related will be summarized for reporting purposes as **Not Related**. For Not Related events, the time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship with study drug, and another cause of the AE (concomitant drugs, therapies, complications, etc.) is suspected.

The relationship categories of possibly, probably, and definitely related will be summarized for reporting purposes as **Related**. Only AEs thought to be caused by the study drug should be classified as "related to study drug." For Related events, the time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship, and no other cause (concomitant drugs, therapies, complications, etc.) can be identified. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.5 Reporting Procedures

10.5.1 Reporting Adverse Events

Adverse events, whether reported by the patient or observed by the investigator/study personnel, must be documented in the patient's medical record and reported by recording all pertinent information on the appropriate eCRF Form in the electronic data capture (EDC) system.

Adverse events, regardless of causality assessment, must be collected beginning from the time the patient signs the ICF until the last study visit or 30 days after the last dose of study drug, whichever is longer.

All AEs must be followed until resolution, or if resolution is unlikely until stabilization.

10.5.2 Reporting Serious Adverse Events

10.5.2.1 Initial Serious Adverse Event Reports

All information regarding SAEs, whether reported by the patient or observed by the investigator/study personnel, must be documented in the patient's medical record and reported by recording all pertinent information on the SAE Forms in the EDC system.

Serious AEs, regardless of causality assessment, must be collected beginning from the time the patient signs the ICF until the last study visit or 30 days after the last dose of study drug, whichever is longer. Any SAE judged by the investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Study site personnel should complete the eCRF SAE Form in the EDC system and the investigator should assess the causality **within 24 hours (without delay, for France only)** of knowledge of the event (this refers to any AE that meets any of the aforementioned seriousness criteria). When the form is completed, Medpace Clinical Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the EDC system is unavailable, the SAE will be reported to Medpace Clinical Safety via email or telephone (see safety contact information below) and the completed form will be sent to Medpace by fax/email (see safety contact information below) within 24 hours of awareness (without delay, for France only). When the EDC system becomes available, the SAE information must be entered within 24 hours (without delay, for France only) of the system becoming available.

The minimum information required for the initial SAE report is covered by the eCRF SAE Form. If requested by Clinical Safety, SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents (see Follow-up Reports, below).

Safety contact information for this study is as follows:

Medpace SAE reporting line – USA

Phone: +1-513-579-9911, dial "3"
Fax: +1-513-570-5196
Email: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe
Phone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
Email: medpace-safetynotification@medpace.com

For urgent safety issues, call the Medical Monitor:

Michael S. Oldham, MD, MPH
Medical Director
Medpace
5375 Medpace Way
Cincinnati, Ohio 45227
Phone: +1 513 579 9911, ext. 11080
Mobile: +1 513 448 6925
Fax: +1 513 579 0444
Email: m.oldham@medpace.com

Marco JD Tangelder, MD, PhD
Senior Medical Director
Medpace
5375 Medpace Way
Cincinnati, Ohio 45227
Home office: Haarlem, the Netherlands
Mobile: +31 620154282
Email: m.tangelder@medpace.com

10.5.2.2 Follow-up Serious Adverse Event Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours (without delay, for France only) of receipt of follow-up information, the investigator must update the eCRF SAE Form within the EDC system. Any requested supporting documentation (e.g. patient discharge summary or autopsy reports) should be submitted via e-mail at (*medpace-safetynotification@medpace.com)* or fax (+1-513-570-5196 or +49 89 89 55 718 104). If it is not possible to access the EDC system, refer to the procedures outlined above (Section 10.5.2) for initial reporting of SAEs. All personal data must be redacted prior to submission; instead, please provide the study number and the patient identification number (ID) on each document. If the follow-up information changes the investigator's assessment of causality, this should also be updated in the eCRF SAE form.

The investigator should notify the IRB/EC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be filed in the investigator's files for this study.

10.5.3 Reporting of Pregnancy

Please refer to Section 8.1.2.2 for the detailed procedures for pregnancy testing, prevention, and reporting.

10.5.4 Expedited Reporting

The RSI is provided in Section 6.9 of the IB. The RSI is used for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction (SUSAR).

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central EC and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional eight days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned and to the Central EC concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all investigators as required per local regulation.

10.5.5 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error and reports of adverse reactions associated with product complaints.

- **Overdose**: refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied.
  In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the investigator has reason to suspect that the patient has taken additional dose (s);
- **Misuse**: refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects;
- **Abuse**: is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects;
- **Medication Error**: Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional, patient or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error;
- **Product Complaint:** is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (see contact information listed above in Section 10.5.2) within 24 hours (without delay, for France only) of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome should be provided, when available.

10.6 Safety Oversight

A Data Monitoring Committee (DMC) will be utilized in this study to ensure external objective medical and/or statistical review of safety data of the study.

The DMC will be composed of independent experts external to the study and will review safety data on a regular basis.

The DMC will operate under the rules of an approved charter that will define the roles and responsibilities of its members. Following each meeting, the DMC will provide its input to Millendo Therapeutics.

11 ADDITIONAL STUDY ASSESSMENTS

Phase 2b

Additional assessments in the Phase 2b Core Period will include the following:

- Change from baseline in:
  - CgGIS-H score (see Section 19.8 Appendix H) and CGIS-H score (see Section 19.7 Appendix G);
  - CgGIC-H score (see Section 19.5 Appendix E) and CGIC-H score (see Section 19.4 Appendix D);
  - CGI-I score (see Section 19.6 Appendix F);
  - CGI-S score (see Section 19.9 Appendix I);
  - Fasting and postprandial glucose and insulin measurement (profile);
  - Appetite-NRS score;
  - DBC2-P score;
  - PedsQL™ Parent-Proxy age-appropriate Reports score;
  - ZBI score;
  - EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score;
  - BMI;
  - BMI Z-score

- Evaluation of the measurement properties and interpretation of clinically meaningful HQ-CT (see Section 9.1.1) change in the study population using blinded study data and according to a psychometric analysis plan;
- Responder definition using anchor-based methods supplemented with both cumulative distribution function (CDF) and probability density function (PDF) to derive the responder threshold for meaningful change;
- Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.
- Percentage change from baseline in BMI
- Percentage of patients with ≥5% and ≥10% reduction in BMI

Additional assessments in the Phase 2b Extension Period will include the following:

- Change from baseline in:
  - CgGIS-H score (see Section 19.8 Appendix H) and CGIS-H score (see Section 19.7 Appendix G);
  - CgGIC-H score (see Section 19.5 Appendix E) and CGIC-H score (see Section 19.4 Appendix D);
  - CGI-I score (see Section 19.6 Appendix F);
  - CGI-S score (see Section 19.9 Appendix I);
  - Fasting glucose and insulin measurement;
  - DBC2-P score;
  - PedsQL™ Parent-Proxy age-appropriate Reports score;
  - ZBI score;
  - EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score;
  - BMI;
  - BMI Z-score

- Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.
- Percentage change from baseline in BMI
- Percentage of patients with ≥5% and ≥10% reduction in BMI

Phase 3

Additional assessments in the Phase 3 Core Period will include the following:

- Change from baseline in:
  - CgGIS-H score (see Section 19.8 Appendix H) and CGIS-H score (see Section 19.7 Appendix G);
  - CgGIC-H score (see Section 19.5 Appendix E) and CGIC-H score (see Section 19.4 Appendix D);
  - CGI-I score (see Section 19.6 Appendix F);
  - CGI-S score (see Section 19.9 Appendix I);
  - Fasting and postprandial glucose and insulin measurement (profile);
  - Appetite-NRS score;
  - DBC2-P score;
  - PedsQL™ Parent-Proxy age-appropriate Reports score;

  - ZBI score;
  - EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score;
- Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.

Additional assessments in the Phase 3 Extension Period will include the following:

- Change from baseline in:
  - CgGIS-H score (see Section 19.8 Appendix H) and CGIS-H score (see Section 19.7 Appendix G);
  - CgGIC-H score (see Section 19.5 Appendix E) and CGIC-H score (see Section 19.4 Appendix D);
  - CGI-I score (see Section 19.6 Appendix F);
  - CGI-S score (see Section 19.9 Appendix I);
  - Fasting glucose and insulin measurement;
  - DBC2-P score;
  - PedsQL™ Parent-Proxy age-appropriate Reports score;
  - ZBI score;
  - EQ-5D-5L Self score and EQ-5D-5L Proxy version 1 score;
- Percentage of HQ-CT responders as defined by anchor-based and distribution-based methods.

11.1 Fasting and Postprandial Glucose, Insulin, Acylated Ghrelin, and Unacylated Ghrelin Profile

Patients will be required to fast for approximately 8 hours before visits requiring fasted blood sampling.

During the Phase 2b Core Period and Phase 3 Core Period, blood levels of glucose, insulin, ghrelin, and UAG will be measured for patients 8 to 65 years of age at the following timepoints:

- Before isocaloric breakfast (and before dosing);
- 30 minutes post-start of breakfast;
- 180 minutes post-start of breakfast.

During the Phase 2b Core Period (patients 4 to 7 years of age), Phase 2b Extension Period and Phase 3 Extension Period, blood levels of fasting glucose, insulin, ghrelin, and UAG will be measured.

11.2 Patient-reported Appetite Following Breakfast: Appetite-Numeric Rating Scale

During the Core Period only, and for patients 8 to 65 years of age only, isocaloric breakfast will be provided, and patients will be asked to rate appetite/prospective food consumption using an appetite-NRS that has been specifically designed for the population of patients with PWS (see Section 19.3 Appendix C).

Completion of this scale will be performed under the supervision of the study personnel (assessments at the study center) before breakfast (after fasting for approximately 8 hours, and before dosing/before any blood sampling when applicable), at the end of breakfast, and 120 minutes post-start of an isocaloric breakfast (see below), except at the screening visit, where the NRS will be administered for training and acclimation purposes (no profile).

With the exception of the randomization visit (visit 2), when the NRS is to be administered, the study drug should be administered 30 minutes before breakfast.

At visits when appetite-NRS assessment will be performed, patients will be given an isocaloric breakfast of 300 to 350 kcal (for patients 8 to 12 years of age) or 350-400 kcal (for patients >12 years of age). This breakfast will be composed of 60% carbohydrates; 25% lipids; 15% proteins. Breakfast must have the same number of calories and must be comparable in composition between days. Patients are encouraged to finish the entire breakfast. Any food not consumed needs to be recorded and reported in the eCRF. Breakfast should not last more than 30 minutes.

The appetite-NRS administration guidelines will be provided in a separate document.

11.3 Effects on Non-Food-Related Behavior: Developmental Behavior Checklist 2-Parent/Carer version

The DBC2-P is a 96-item instrument completed by parents or other primary caregivers, used for the assessment of behavioral and emotional problems in people with developmental and intellectual disabilities. The DBC2-P will be completed by the patients' primary caregiver.

11.4 Effects on Patients' Quality of Life: PedsQL™ 4.0 Generic Core Scales

The QoL of participants will be assessed through the parent-proxy PedsQL™ 4.0 report (68-73) (Section 19.10 Appendix J). The PedsQL™ measurement model is a brief, standardized assessment instrument that systematically assesses HRQoL through child self-reports. In this study, considering that patients with PWS have cognitive impairment, the parent proxy report scale will be used, in accordance with PedsQL™ 4.0 administration guidelines. The PedsQL™ 4.0 Generic Core Scale consists of 23 items applicable to a healthy school and community populations, as well as pediatric populations with acute and chronic health conditions. It encompasses: 1) physical functioning (eight items); 2) emotional functioning (five items); 3) social functioning (five items); and 4) work/studies functioning (five items).

PedsQL™ 4.0 Parent-Proxy age-appropriate Reports will be used for all patients and will be completed by the patients' primary caregiver.

11.5 Effects on Caregiver Burden: Zarit Burden Interview

The ZBI is a self-reported outcome that was designed to assess the level of burden experienced by the principal caregiver of individuals with disabilities (Section 19.11 Appendix K). This questionnaire will be completed by the patients' primary caregiver.

12 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Millendo Therapeutics or its designee;
- At the monitoring visits, the progress of the study will be discussed with the investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Patient source data must be available for review. The investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information;
- The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the investigator in writing;
- Telephone contact will be made with the investigator as necessary during the data collection period and during the data and report writing periods;
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

13 STATISTICAL CONSIDERATIONS

Complete details of the analysis plan will be provided in the Statistical Analysis Plan (SAP) related to each Phase and Period (Phase 2b Core Period, Phase 2b Extension Period, Phase 3 Core Period, and Phase 3 Extension Period).

Any deviations from, or additions to, the original analysis plan in this protocol will be documented in the SAPs and the clinical study report(s).

13.1 Statistical Hypotheses

Safety data will be presented descriptively, thus no formal hypothesis for safety will be tested. Efficacy endpoints will be tested with hypothesis of the form:

$H0: \mu_{Test} = \mu_{Placebo}$

$H1: \mu_{Test} \neq \mu_{Placebo}$ for continuous variables

$H0: \pi_{Test} = \pi_{Placebo}$

$H1: \pi_{Test} \neq \pi_{Placebo}$ for categorical variables

where μ is the mean in the population and π is the proportion in the population.

13.2 Sample Size Determination

13.2.1 Phase 2b

In the completed Phase 2a study (2 weeks of treatment), the change from baseline to Day 14 in the 9-item score of the HQ was -4.3 units for livoletide and -1.6 units for placebo, with a difference between groups of 2.7 units.

For the Phase 2b Core Period (N=150, 8- to 65-year-olds), a between group difference of 4 units in the change from baseline in the HQ-CT score has been selected for sample size calculation based on the following:

1. It is considered reasonable to achieve this difference as a 3 months treatment period is expected to produce a higher effect as compared to short-term treatment (2 weeks).
2. It is in line with the HQ-CT distribution-based estimates of meaningful change observed in a landmark Phase 3 clinical trial (74) that included 107 obese individuals with PWS 12 to 65 years of age (half-standard deviation [SD]=3.3, standard error of the mean [SEM]=4.4). In addition, the distribution-based estimates were found to be approximately the magnitude of the difference between the mean change of the "A little better" and "No change" in the CGIC subgroups.

Assuming a 2-sided parametric test, alpha of 2.5% (Bonferroni adjustment for 2 comparisons) and a SD of 5, forty-one (41) patients per group will allow to detect a difference between groups of at least 4 units in the primary endpoint 9-item score of the HQ-CT. This is considered a conservative approach as higher is the difference between groups, lower is the sample size.

Assuming a drop-out rate at 3 months of about 18%, a total of 50 patients (8 to 65 years of age) per group will need to be randomized.

There is no formal sample size calculation done for patients in the 4 to 7 year of age cohort since data for subjects in this cohort will be considered supportive (i.e. this cohort will not be included in the Phase 2b primary endpoint analysis).

Randomization will be stratified to ensure there are at least 25 patients (8 to 65 years of age) who are overweight/obese per treatment group.

13.2.2 Phase 3

For Phase 3, the total number of required patients to be randomized is estimated to be 50 patients per group. Final sample size will be determined following analysis of data at the completion of the Phase 2b Core Period.

13.3 Concept of Estimands and General Strategy for Analyses

As per the ICH E9 Addendum, an estimand defines in detail what needs to be estimated to address a specific scientific question of interest. In this study, the specific question or objective is to demonstrate the efficacy of a 3-month (or 6-month) treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior. As described in Figure 8 below, a description of an estimand includes four attributes:

A. the population, that is, the patients targeted by the scientific question;

B. the variable (or endpoint), to be obtained for each patient, that is required to address the scientific question;

C. the specification of how to account for intercurrent events to reflect the scientific question of interest.

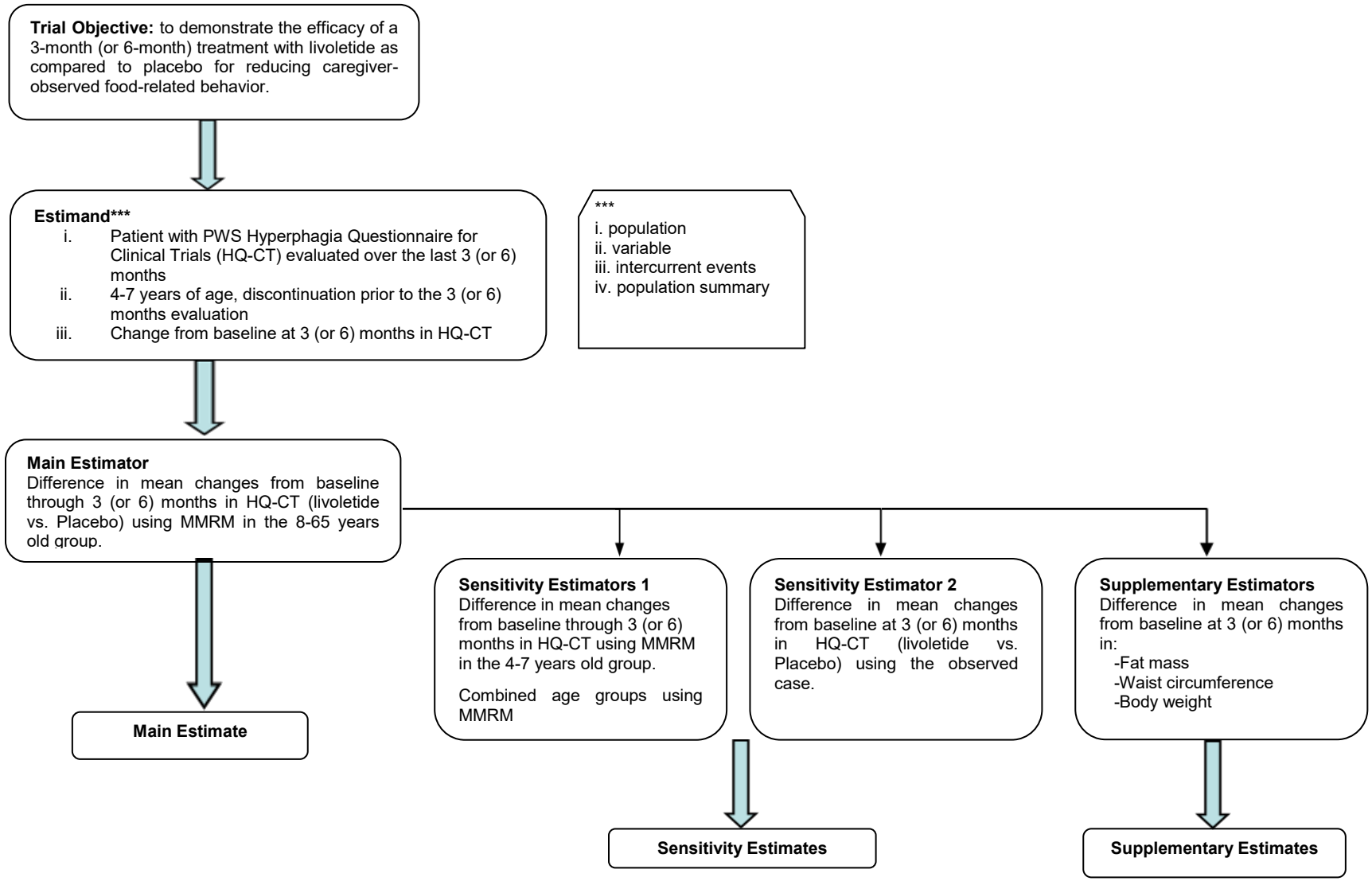
D. the population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions.

In this study, the main two intercurrent events identified are the missing observations caused par patients dropping out before their 3 months (for the phase 2b) or their 6 months (for the phase 3) evaluation and the younger age group of 4-7 years old who might not behave similarly to the older group.

The main estimator will be based on the 8-65 years old group using an MMRM approach to handle the missing observations. Sensitivity analyses will present the results in the subgroup of 4-7 years old patients separately, as well as combined with the 8-65 years old patients. Moreover, additional sensitivity analyses will be performed on observed cases at 3 months (for the phase 2b) or 6 months (for the phase 3) to evaluate the robustness of the missing observations strategy using the MMRM approach in the 8-65 years old group.

Supplementary analyses will consist of the analyses of the key secondary endpoints in a manner similar to the main estimator (i.e. MMRM in the 8-65 years old group). They will also consist of the statistical analyses of all additional study assessments as described in section 11. These supplementary analyses will all be supportive in providing additional insights into the understanding of the treatment effect.

Figure 8: General concept of estimands in the Phase 2b and Phase 3 studies



13.4 Populations for Analyses

Populations will be derived for each Phase and Period (Phase 2b Core Period, Phase 2b Extension Period, Phase 3 Core Period, and Phase 3 Extension Period) with the exception of the PK population, which will be defined for the Phase 2b Core and Extension Periods.

13.4.1 Full Analysis Set

All randomized patients will be included in the Full Analysis Set (FAS). The initial randomization will be preserved for this analysis set in order to comply with the Intent-To-Treat (ITT) principle.

13.4.2 Per Protocol

The Per Protocol set (PP) will include all randomized patients who:

- Completed the period of treatment (i.e. 3 months [Phase 2b Core Period], 6 months [Phase 3 Core and Extension Periods] or 9 months [Phase 2b Extension Period]);
- Have non-missing observation at baseline and at the end of the period for the primary efficacy endpoint;
- Have no major protocol violations including the violation of inclusion/non-inclusion criteria.

The treatment actually received by the patient will be used in this set. Prior to database lock, major protocol violations will be defined and reviewed by Millendo Therapeutics and the CRO in charge of the study follow-up in a blinded fashion. Patients with major protocol violations will be excluded from the PP population(s).

13.4.3 Safety Population

All randomized patients who received at least one dose of study drug will be included in the Safety population. Patients will be analyzed as per the treatment they received.

13.4.4 Pharmacokinetic Population

All randomized patients who received at least one dose of study drug and for whom robust PK data can be obtained will be included in the PK population.

13.5 Statistical Analyses

All continuous variables will be summarized by presenting the number of patients, mean, SD, median, minimum, and maximum. Categorical variables will be presented as frequencies and percentages.

Efficacy analyses will be performed on the FAS as main analyses and on PP population, as supportive analyses. Safety analyses will be performed on the Safety population.

Methods to control for the overall type 1 error for multiple testing will be described in detail in the SAPs.

For efficacy endpoints, handling of missing observations will be done using the mixed model repeat measures (MMRM) approach. No imputation of missing observations will be done for safety parameters.

For all statistical efficacy analyses, the distribution of efficacy the residuals will be visually examined to determine whether substantial departures from normality and homogeneity of variance are apparent. If the data are inconsistent with the assumption of normality and homogeneity of variance, alternative non-parametric models may be presented instead.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be presented in separate SAPs that will be prepared before the database is locked and any analyses are undertaken.

13.5.1 Phase 2b

13.5.1.1 Analysis of the Efficacy Endpoints

Core Period

The primary analysis for the primary efficacy endpoint will be done using a mixed model repeated measures analysis (MMRM) on the change-from-baseline HQ-CT total score within the first 3-months. The model will include treatment, visit, stratification variables, and treatment by visit interaction as fixed effects and baseline score as a covariate. An unstructured covariance will be used to model the correlation. In the case where convergence issues arise, the autoregressive (AR (1)) structure will be used. Contrasts will be defined in the mixed model to test for treatment differences at different time points, but the primary comparison will be done at 3-months.

As supportive analysis, an analysis of covariance (ANCOVA) on the change-from-baseline HQ-CT total score at 3 months will be performed. The model will include treatment and the stratification variables as fixed effects, and HQ-CT total score at baseline as a covariate.

The key secondary endpoints percentage change from baseline in total body fat mass, change from baseline in WC, and percentage change from baseline in BW on overweight/obese patients will be analyzed using the same approach as for the primary efficacy endpoint. In addition, as exploratory analyses, the analyses will also be performed based on all patients, including BMI (categorical variable) in the statistical models.

Sensitivity analyses will be performed on the 4-7 years old group separately and combined with the 8-65 years old group, using MMRM models.

Extension Period

The change from baseline to the end of the 9-month Extension Period in HQ-CT total score and the change from the end of the 3-month Core Period to the end of the 9-month Extension Period in HQ-CT total score will be compared using an MMRM approach. The dependent variable will be HQ-CT total score. The model will include treatment, stratification variables, and treatment by visit interaction. An unstructured variance-covariance matrix will be used to model the intra-patient correlation. In the case where convergence issues arise, the autoregressive (AR (1)) structure will be used. Contrasts will be defined in the mixed model to test 12 months vs 3 months and 12 months vs baseline, per treatment.

Percentage change from baseline in total body fat mass, change from baseline in WC, and percentage change from baseline in BW will be analyzed using the same approach as described above on overweight/obese patients.

13.5.1.2 Analysis of the Additional Assessments

Similar statistical approaches as described in Section 13.5.1.1 will be used for the analyses of the additional assessments being continuous variables. Responders will be analyzed using a Pearson-Chi Squared test.

13.5.1.3 Safety Analyses

Results from the Core and the Extension Periods will be presented separately.

Adverse Events:

Adverse events will be collected from the time of signing of informed consent. Adverse events will be classified as TEAEs or pre-treatment AEs. An AE with an unknown/unreported onset date will also be counted as a TEAE. Unless otherwise stated, all references to Aes in this study protocol refer to TEAEs. An increase of intensity or frequency of a pre-treatment AE will also be considered as a TEAE.

The number and percentage of patients, who experience TEAEs, will be presented by System Organ Class (SOC) and by Preferred Term (PT) within SOC for each treatment group. TEAEs will be similarly presented by severity and by relationship to study drug. TEAEs will be presented for each group. The total number of TEAEs, as well as the total number of patients with TEAEs, will also be presented. Treatment-emergent SAEs (TESAEs) will be presented similarly as TEAEs.

A patient experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a patient experiences multiple Aes within the same SOC, the patient will be counted only once for that SOC. If a patient experiences more than one AE within different severity or relationship categories within the same SOC/PT, only the worst case (worst severity and related AE) will be reported. Aes will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order of total frequency. Aes will be coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA).

A listing of SAEs and discontinuations due to Aes will be presented. Patient deaths will be listed separately. SAEs and discontinuations due to Aes will be described by case narratives. All Aes will be presented by investigative site and by treatment group in a listing, which will include the patient identifier, PT, reported term, severity, seriousness, action taken, outcome, relationship, date of onset, duration, end date, and study treatment at the time of the event of most recent study treatment taken. Separate listings will be provided for pre-treatment and post-treatment events.

Safety Laboratory Evaluations

Descriptive statistics (n, mean, SD, median, and range) for each clinical laboratory test will be presented by treatment group and available visit. Change from baseline to each available post dose visit will also be summarized.

According to the laboratory normal ranges, laboratory test results will be categorized as low (< lower normal limit), normal (within normal range), and high (> upper normal limit). Shift tables comparing the distributions of these three categories at baseline versus each available post-dose visit will be presented by treatment group for key safety laboratory evaluations.

Moreover, a summary of newly occurring or notable worsening laboratory abnormalities will be presented. The criteria to identify these laboratory abnormalities will be defined in the SAP(s).

Vital Signs and Electrocardiograms

Descriptive statistics (n, mean, SD, median, and range) will be presented by treatment group and available visits. Change from baseline to each available post-dose visit will also be summarized.

Physical Examinations

Physical exam will be summarized by visit in terms of n (%) of patients with normal/abnormal results per body system and treatment group. Moreover, shift tables from baseline to the end of each period will be presented.

Lean Body Mass and Bone Mineral Density

Descriptive statistics (n, mean, SD, median, and range) will be presented by treatment group and available visits for lean body mass and bone mineral density results. Change and percent change (for lean body mass) from baseline to each available post-dose visit will also be summarized.

13.5.1.4 Planned Interim Analyses (if applicable)

No interim analysis is planned in Phase 2b.

13.5.2 Phase 3

Statistical analyses to be performed in Phase 3 (Core and Extension Periods) will be comparable to those performed in Phase 2b and will be further described at a later stage.

13.6 Sub-group Analyses

13.6.1 Phase 2b

Primary efficacy endpoint HQ-CT total score will also be analyzed by subgroups of age (4 to 7 years of age, 8 to 17 years of age, and ≥18 years of age) and BMI (patients ≥18 years of age: BMI <27 kg/m^2 vs BMI ≥27 kg/m^2; patients 4-17 years of age: BMI <90^{th} percentile vs BMI ≥90^{th} percentile for the same age and sex).

Analyses on blood glucose and insulin will be performed on all population and on patients with elevated postprandial glucose (EPG). EPG is defined as 1-hour post-meal glucose concentration ≥8.0 mmol/L (144 mg/dL).

13.6.2 Phase 3

Sub-group analysis to be performed in Phase 3 (Core and Extension Periods) will be further described at a later stage.

13.7 Analyses of HQ-CT Measurement Properties

The analyses of HQ-CT measurement properties will be described in a specific separate document.

13.8 Analysis of Pharmacokinetic Samples

Plasma livoletide PK parameters will be derived using non-compartmental methods.

Where possible, the following PK parameters will be determined. Additional parameters may also be calculated as appropriate.

Maximum concentration (C_{max}); time of C_{max} (t_{max}); observed minimum concentration (C_{min}); time of C_{min} (t_{min}); average concentration during the dosing interval (C_{avg}); fluctuation index over the dosing interval (FI); area under the concentration-time curve during the dosing interval ($AUC_{(0\text{-}tau)}$); apparent terminal rate constant (λz); apparent terminal half-life ($t_{1/2}$); apparent total body clearance (CL/F); apparent volume of distribution (Vz/F); accumulation ratio for $AUC_{(0\text{-}tau)}$ ($RAUC_{(0\text{-}tau)}$); accumulation ratio for C_{max} (RC_{max}); and linearity index (LI) as appropriate.

The linear up/log down trapezoidal method will be used for calculation of all PK areas under the curve. Further details of the PK analyses will be described in a separate PK SAP. The plasma concentrations obtained during this study may be used for a stand-alone population-PK model that will be reported separately.

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with International Council for Harmonisation (ICH GCP) Guidelines and regulatory and institutional requirements for the protection of confidentiality of participants.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable for the eCRF to be the only record of a patient's participation in the study. This is to ensure that anyone who accesses the patient medical record is adequately informed that the patient is participating in a clinical trial.

15 QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted in compliance with the protocol, current GCP rules, and the applicable regulatory requirements.

Quality Control comprises the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s). As part of the supervision of the study progress, the Sponsor personnel or the CRO may, on request,

accompany the monitor on visits to the study site. The investigator and the study investigator collaborators commit to cooperate with the monitor to resolve any problems, corrections, or possible misunderstandings concerning the findings or protocol violations detected in the course of these monitoring visits.

Protocol violations will be sorted in significant and non-significant violations before the blind data review. A significant violation is any violation identified during monitoring that requires immediate information to the Sponsor for possible action (for example, withdrawal of the patient from the study).

During the data review and before unblinding, protocol violations will be sorted in major and minor violations. A major violation is any violation having an impact on the classification of the population sets (for example, impacting the main evaluation criteria).

Site personnel will be trained on the condition to be treated, the protocol, and all study-specific procedures. They will be provided with specific instructions.

16 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

16.1 Regulatory, Ethical, And Study Oversight Considerations

The investigator will ensure that this study is conducted in full conformity with ICH GCP E6 principles, the Declaration of Helsinki (1964) and all subsequent amendments as amended (see Section 19.1 Appendix A), and all other applicable regulatory requirements.

16.2 Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the Sponsor or its designate), relevant supporting information, and patient recruitment materials to the IRB/EC for review. All must be approved prior to site initiation. Prior to implementing changes in the study, the Sponsor and the IRB/EC must also approve any revised ICFs and/or protocol amendments.

On the IRB/EC approval letter, the study reference number the date of review and actions taken should be clearly stated.

Study drug will not be released to the site and recruitment of patients will not begin until the IRB/EC written approval has been received by the Sponsor or its designee.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol and/or ICF. The investigator must also keep the IRB/EC informed of any serious and significant AEs, as per country regulation.

16.3 Informed Consent Process

According to local requirements and GCP, prior to participation in the study, the investigator must fully explain orally to each patient and legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort or constraint it may entail. The patient and legally authorized representative should be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. Each patient must be informed that participation in the study is voluntary and that he or 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.

The ICF is documented by means of a written, signed, and dated patient/legally authorized representative consent form (or age-appropriate assent form) per local requirements, prior to the start of the study. Age-appropriate assent forms will be completed for minor patients. The Informed Consent/Assent Form will be written in a language and in a form understandable to the patient/legally authorized representative. This assent form will be dated and signed by the patient insofar as possible. In all cases, the first name and last name will be asked to be mentioned by the patient.

One signed and dated copy of the ICF will be given to the patient/parent and one signed and dated original copy will be maintained by the investigator in the study file in compliance with ICH E6 and local regulations.

The investigator should clearly indicate the patient's participation in a clinical trial in his/her medical chart. No patient can have a study-related procedure performed before informed consent has been obtained. The assistance of the legally acceptable representative will also be documented in the patient medical chart.

The Informed Consent/Assent Form is part of the protocol and must be submitted for IRB/EC approval. Millendo Therapeutics or designee will supply a proposed Informed Consent/Assent Form, that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent/assent form suggested by the investigator must be agreed to by Millendo Therapeutics or designee before submission to the IRB/EC and a copy of the approval version must be provided to Millendo Therapeutics or designee after IRB/EC approval. In addition, any change that may affect patients' participation and/or safety will necessitate patients to re-consent.

16.4 Participants' and Data Confidentiality

Patient confidentiality is strictly held in trust by the Sponsor and/or their designee(s), participating investigators, and any staff. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

Any research information obtained about the patient in this study will be kept confidential in accordance with all relevant national and international laws governing data privacy and security. A patient will not be identified by name, only by his/her initials. The patient's name or any other identifying information will not appear in any reports published as a result of this study.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. However, information obtained from individual patient's participation in the study may be disclosed with his/her express written consent to the health care providers for the purpose of obtaining appropriate medical care. The patient's medical records/charts and tests with his/her name on them may be made available to the appropriate CRO, the Sponsor, its potential eventual partners, and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked

doors, under the supervision of the study investigator, and will not be transferred outside of the investigator site

The study monitors or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The study site will permit access to such records.

A patient may take away his/her permission to collect, use, and share information about him/her at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

17 DATA HANDLING AND RECORD KEEPING

17.1 Data Collection and Management Responsibilities

The Sponsor or its designee will instruct the study center regarding data capture procedures on eCRF.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source documentation supporting the data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

The investigator, or designated representative, should complete data entry as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and selected clinical laboratory data will be entered into Clintrak EDC, a 21 Code of Federal Regulations (CFR) Part 11-compliant data capture system provided by the Clintrak EDC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

17.2 Study Records Retention

To enable evaluations and/or audits from the regulatory authorities, the appropriate CRO, or the Sponsor, the investigator agrees to keep records, including the identity of all participating

patients (sufficient information to link records, eCRFs, and hospital records), all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition. The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain written permission from the Sponsor before disposing of any records.

It is recommended that the Sponsor or designee retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial, or a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

If the Sponsor's situation is such that archiving cannot be ensured, Sponsor shall transfer his responsibility for archiving to a mutually agreed designee.

17.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4;
- 5.1 Quality Assurance and Quality Control, section 5.1.1;
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the investigator and the Sponsor and approved by the IRB/EC, except for patient safety as noted below. Investigative sites will contact the medical monitor to request clarifications regarding any aspect of the clinical study or eligibility of patients.

When an emergency occurs that requires a deviation from the protocol for an individual patient, the deviation will be only for that patient. The investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor or their representative(s), immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the patient (for whom the protocol deviation was affected) is to continue in the study. The source documentation will completely describe the protocol deviation and state the reasons for such deviation. In addition, the IRB/EC will be notified in writing of such protocol deviation, as appropriate.

17.4 Protocol Amendments

Any change or addition to this protocol requires a written protocol amendment that must be approved by Millendo Therapeutics and the Coordinating PI before implementation.

Amendments significantly affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/EC, and, when applicable, by the regulatory authority. A copy of the written approval of the IRB/EC, which becomes part of the protocol, must be given to Millendo Therapeutics.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Millendo Therapeutics in the interest of preserving the safety of all patients included in the trial.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/EC approval but the IRB/EC of each center must be kept informed of such administrative changes (e.g. correcting for typographical errors, rewording for clarity, changes in study personnel).

17.5 Publication and Data Sharing Policy

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered a joint publication by the investigators and the appropriate personnel of Millendo Therapeutics. It is mandatory that the first publication is based on all data obtained from all analyzed patients as stipulated in the protocol. Participating investigators must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication. Authorship will be determined according to Millendo Therapeutics publication policy and in agreement with the coordinating PI. The latter will be the last author and co-authorship will be based on substantial contributions to study conception and design and/or analysis and interpretation of data in accordance with the Vancouver protocol, as well as on recruitment performance when applicable.

Millendo Therapeutics will manage the process of preparing abstracts, posters, and manuscripts for the joint publications that include data from all centers. For any other intended communication on the data from this study, Millendo Therapeutics requests to receive copies in advance (at least 15 working days for an abstract or oral presentation and 45 working days for a manuscript). This is to allow Millendo Therapeutics to review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not being inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship.

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.

A summary of the study results will be made publicly available within 12 months of reaching the end of the study, defined as the date of the LPLV. A full clinical study report will be made publicly available no later than 18 months after the end of the study.

17.6 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have

a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

17.7 Financing and Insurance

In accordance with the provisions of the law and the GCP principles, the Sponsor will subscribe to an insurance policy covering, in its terms and conditions, its legal liability for certain injuries to participating persons arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

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Abbreviation or Term	Definition
°C	Celsius degree
°F	Fahrenheit degree
µg	microgram
ADA	anti-drug antibodies
AE	adverse event
AG	acylated ghrelin
AgRP	agouti-related protein
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0\text{-}tau)}$	area under the concentration-time curve during the dosing interval
AZP-531	livoletide
BID	twice daily
BMI	body mass index
BW	body weight
C_{avg}	average concentration during the dosing interval
C_{max}	maximum concentration
C_{min}	observed minimum concentration
CDF	cumulative distribution function
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CgGIS-H	Caregiver Global Impression of Severity - Hyperphagia
CGIS-H	Clinical Global Impression of Severity - Hyperphagia
CgGIC-H	Caregiver Global Impression of Change - Hyperphagia
CGIC-H	Clinical Global Impression of Change – Hyperphagia
CHF	congestive heart failure
CL/F	apparent total body clearance

CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRO	Clinical Research Organization
CTA	Clinical Trial Authorization
CFR	Code of Federal Regulations
DBC2-P	Developmental Behavior Checklist 2-Parent/Carer version
DBP	diastolic blood pressure
DXA	dual energy X-ray absorptiometry
dL	deciLiter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eDevice	electronic device
EIU	Exposure In Utero
e.g.	exempli gratia
EMA	European Medicine Agency
EPG	Elevated Postprandial Glucose
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
FI	fluctuation index over the dosing interval
FISH	fluorescence *in situ* hybridization
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GHSR	Growth Hormone Secretagogue Receptor
GLP	Good Laboratory Practice
GLP-1	glucagon-like-peptide 1
GMP	Good Manufacturing Practice
GOAT	ghrelin O-acyltransferase

HbA1c	glycated hemoglobin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HQ	Hyperphagia Questionnaire
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HR	heart rate
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification number
i.e.	id est
IGF-1	insulin-like growth factor-1
IND	Investigational New Drug
IQ	Intelligence Quotient
IRB	Institutional Review Board
ITT	Intent-To-Treat
IRT	Interactive Response Technology
kg	kilogram
λ_z	apparent terminal rate constant
L	Liter
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	luteinizing hormone
LI	linearity index
LPLV	last visit of the last patient
MAD	multiple ascending dose
MC3R	melanocortin-3 receptor
MC4R	melanocortin-4 receptor
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction

mg	milligram
mmHg	milliliter of mercury
MMRM	mixed-effect model repeat measurement
mL	milliliter
N	number of patients
NaCl	sodium chloride
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
NYHA	New York Heart Association
OECD	Organization for Economic Co-operation and Development
PedsQL™	Pediatric Quality of Life inventory™
PD	pharmacodynamic
PDF	probability density function
PI	Principal Investigator
PK	pharmacokinetics
PP	Per Protocol
PT	Preferred Term
PWS	Prader-Willi Syndrome
QoL	Quality of Life
QT_CB	QT interval corrected for HR by Bazett's formula
QT_CF	QT interval corrected for HR by Fridericia's formula
$RAUC_{(0\text{-}tau)}$	accumulation ratio for $AUC_{(0\text{-}tau)}$
RC_{max}	accumulation ratio for C_{max}
REB	Research Ethics Board
RSI	reference safety information
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class

SOP	Standard Operating Procedure
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	apparent terminal half-life
t_{max}	time of C_{max}
t_{min}	time of C_{min}
T2D	type 2 diabetes
tbc	to be confirmed
TEAE	treatment-emergent adverse event
UAG	unacylated ghrelin
ULN	upper limit of normal
US	United States
V	visit
V_z/F	apparent volume of distribution
vs	versus
WC	waist circumference
WCBP	Women of Child Bearing Potential
ZBI	Zarit Burden Interview

19 APPENDICES

19.1 APPENDIX A: Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and all subsequent amendments.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of The World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the Sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to

abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical re-search involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

19.2 APPENDIX B: Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Instructions:
The following items refer to the person in your care and assessment of his/her food-related behavior during the past 2 weeks.

(1) During the past 2 weeks, how upset did the person generally become when denied a desired food?

□ Not at all upset
□ A little upset
□ Moderately upset
□ Very upset
□ Extremely upset

(2) During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

(3) During the past 2 weeks, how often did the person forage through trash for food?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(4) During the past 2 weeks, how often did the person get up at night to food seek?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(5) During the past 2 weeks, how persistent was the person in asking or looking for food after being told "no" or "no more"?

□ Not at all persistent
□ A little persistent
□ Moderately persistent
□ Very persistent
□ Extremely persistent

(6) During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?

□ Less than 5 minutes a day
□ 5 to 15 minutes a day
□ 15 to 30 minutes a day
□ 30 minutes to 1 hour a day
□ More than 1 hour a day

(7) During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(8) During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?

□ Not at all distressed
□ A little distressed
□ Moderately distressed
□ Very distressed
□ Extremely distressed

(9) During the past 2 weeks, how often did food-related behavior interfere with the person's normal daily activities, such as self-care, recreation, school, or work?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

19.3 APPENDIX C: Numerical Rating Scale (NRS) for Appetite/Prospective Food Consumption

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Patient number: |__|__|__|__|__| |__|__|

Test date:

Meal: ☐ **Breakfast** ☐ **Lunch**

Time of the test: ☐ **Before** ☐ **After** ☐ **2**

Indicate how much food you could eat right now, by checking the appropriate box

Nothing at all	**A small amount**	**A medium amount**	**A large amount**	**A very large amount**
☐	☐	☐	☐	☐

19.4 APPENDIX D: Clinical Global Impression of Change – Hyperphagia (CGIC-H) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Clinical Global Impression of Change – Hyperphagia (CGIC-H) Scale

Overall, how would you rate the person's hyperphagia now as compared to before the beginning of the study?

☐ = Much better

☐ = Moderately better

☐ = A little better

☐ = No difference

☐ = A little worse

☐ = Moderately worse

☐ = Much worse

19.5 APPENDIX E: Caregiver Global Impression of Change - Hyperphagia (CgGIC-H) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Caregiver Global Impression of Change - Hyperphagia (CgGIC-H) Scale

Overall, based on your observations, how would you rate the person's hyperphagia now as compared to before the beginning of the study?

☐ = Much better

☐ = Moderately better

☐ = A little better

☐ = No difference

☐ = A little worse

☐ = Moderately worse

☐ = Much worse

19.6 APPENDIX F: Clinical Global Impression of Improvement (CGI-I) Scale

Clinical Global Impression of Improvement (CGI-I) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Overall, how would you rate the person's general condition now as compared to before the beginning of the study?

☐ = Much better
☐ = Moderately better
☐ = A little better
☐ = No difference
☐ = A little worse
☐ = Moderately worse
☐ = Much worse

19.7 APPENDIX G: Clinical Global Impression of Severity – Hyperphagia (CGIS-H) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Clinical Global Impression of Severity – Hyperphagia (CGIS-H) Scale

Overall, how would you rate the severity of the person's hyperphagia now?

☐ = Normal, not at all hyperphagic
☐ = Borderline hyperphagic
☐ = Mildly hyperphagic
☐ = Moderately hyperphagic
☐ = Markedly hyperphagic
☐ = Severely hyperphagic
☐ = Among the most extremely hyperphagic patients

19.8 APPENDIX H: Caregiver Global Impression of Severity - Hyperphagia (CgGIS-H) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Caregiver Global Impression of Severity - Hyperphagia (CgGIS-H) Scale

Overall, based on your observations, how would you rate the person's hyperphagia now?

☐ = None

☐ = Mild

☐ = Moderate

☐ = Severe

19.9 APPENDIX I: Clinical Global Impression of Severity (CGI-S) Scale

Clinical Global Impression of Severity (CGI-S) Scale

The paper version of the questionnaire will be adapted for assessment using the eDevice.

Considering your total clinical experience with this particular population, how would you rate the severity of the person's disease?

☐ = Normal, not at all ill

☐ = Borderline ill

☐ = Mildly ill

☐ = Moderately ill

☐ = Markedly ill

☐ = Severely ill

☐ = Extremely ill

19.10 APPENDIX J: PEDSQL™ PARENT PROXY-REPORTS

The paper version of the questionnaire will be adapted for assessment using the eDevice.

PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France– Internet: https://eprovide.mapi-trust.org and www.pedsql.org/index.html

ID#_____

Date:_____

PedsQL ™

Adult Quality of Life Inventory

Version 4.0

PARENT REPORT for ADULTS

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

Physical Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other adults	0	1	2	3	4
2. Other adults not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other adults	0	1	2	3	4
4. Not able to do things that others his or her age can do	0	1	2	3	4
5. Keeping up with other adults	0	1	2	3	4

Work/Studies Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention at work or school	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with work or studies	0	1	2	3	4
4. Missing work or school because of not feeling well	0	1	2	3	4
5. Missing work or school to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL ™

Adult Quality of Life Inventory

Version 4.0

PARENT REPORT for YOUNG ADULTS (ages 18-25)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

Physical Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other young adults	0	1	2	3	4
2. Other young adults not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other young adults	0	1	2	3	4
4. Not able to do things that others his or her age can do	0	1	2	3	4
5. Keeping up with other young adults	0	1	2	3	4

Work/Studies Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention at work or school	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with work or studies	0	1	2	3	4
4. Missing work or school because of not feeling well	0	1	2	3	4
5. Missing work or school to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL ™

Adult Quality of Life Inventory

Version 4.0

PARENT REPORT for TEENS (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your teen had with …*

Physical Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that others his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

Work/Studies Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL ™

Adult Quality of Life Inventory

Version 4.0

PARENT REPORT for CHILDREN (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

Physical Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up with other children	0	1	2	3	4

Work/Studies Functioning ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL ™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

In the past **ONE month,** how much of a **problem** has your child had with …

Physical Functioning *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

School Functioning (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL ™
Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for TODDLERS (ages 2-4)

20 DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has your child had with …*

Physical Functioning *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

Social Functioning (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

School Functioning (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

20.1 APPENDIX K: Zarit Burden Interview

The paper version of the questionnaire will be adapted for assessment using the eDevice.

BURDEN INTERVIEW

INSTRUCTIONS: The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, indicate how often you feel that way; never, rarely, sometimes, quite frequently, or nearly always. There are no right or wrong answers.

1. Do you feel that your relative asks for more help than he/she needs?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

4. Do you feel embarrassed over your relative's behavior?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

5. Do you feel angry when you are around your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

6. Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

7. Are you afraid what the future holds for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

8. Do you feel your relative is dependent upon you?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

9. Do you feel strained when you are around your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

10. Do you feel your health has suffered because of your involvement with your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

11. Do you feel that you don't have as much privacy as you would like, because of your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

12. Do you feel that your social life has suffered because you are caring for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

13. Do you feel uncomfortable about having friends over, because of your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

14. Do you feel that your relative seems to expect you to take care of him/her, as if you were the only one he/she could depend on?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

15. Do you feel that you don't have enough money to care for your relative, in addition to the rest of your expenses?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

16. Do you feel that you will be unable to take care of your relative much longer?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

17. Do you feel you have lost control of your life since your relative's illness?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

18. Do you wish you could just leave the care of your relative to someone else?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

19. Do you feel uncertain about what to do about your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

20. Do you feel you should be doing more for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

21. Do you feel you could do a better job in caring for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

22. Overall, how burdened do you feel in caring for your relative?

0. Not at all 1. A little 2. Moderately 3. Quite a bit 4. Extremely

20.2 APPENDIX L: Protocol Versions

Protocol Version	Date	Significant Revision
1.0	September 5, 2018	N/A – Initial version
1.1	November 13, 2018	PK design and Screening period duration
1.2	July 31st, 2019	Inclusion of patients 4 to7 years of age to the study