Official Title of Study: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Pitolisant in Patients with Prader-Willi Syndrome, Followed by an Open Label Extension

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Statistical Analysis Plan (SAP)

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Pitolisant in Patients with Prader-Willi Syndrome, Followed by an Open Label Extension
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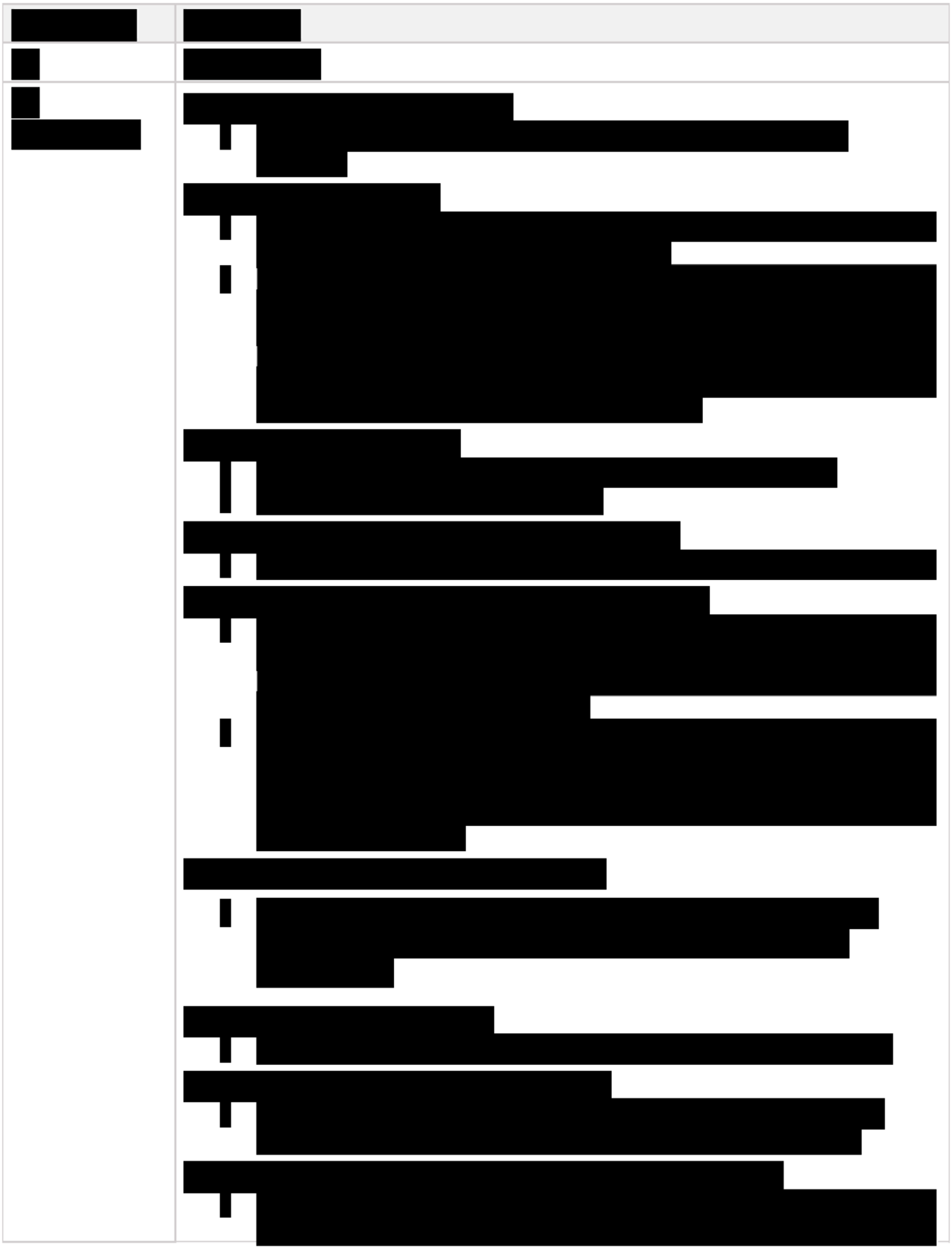
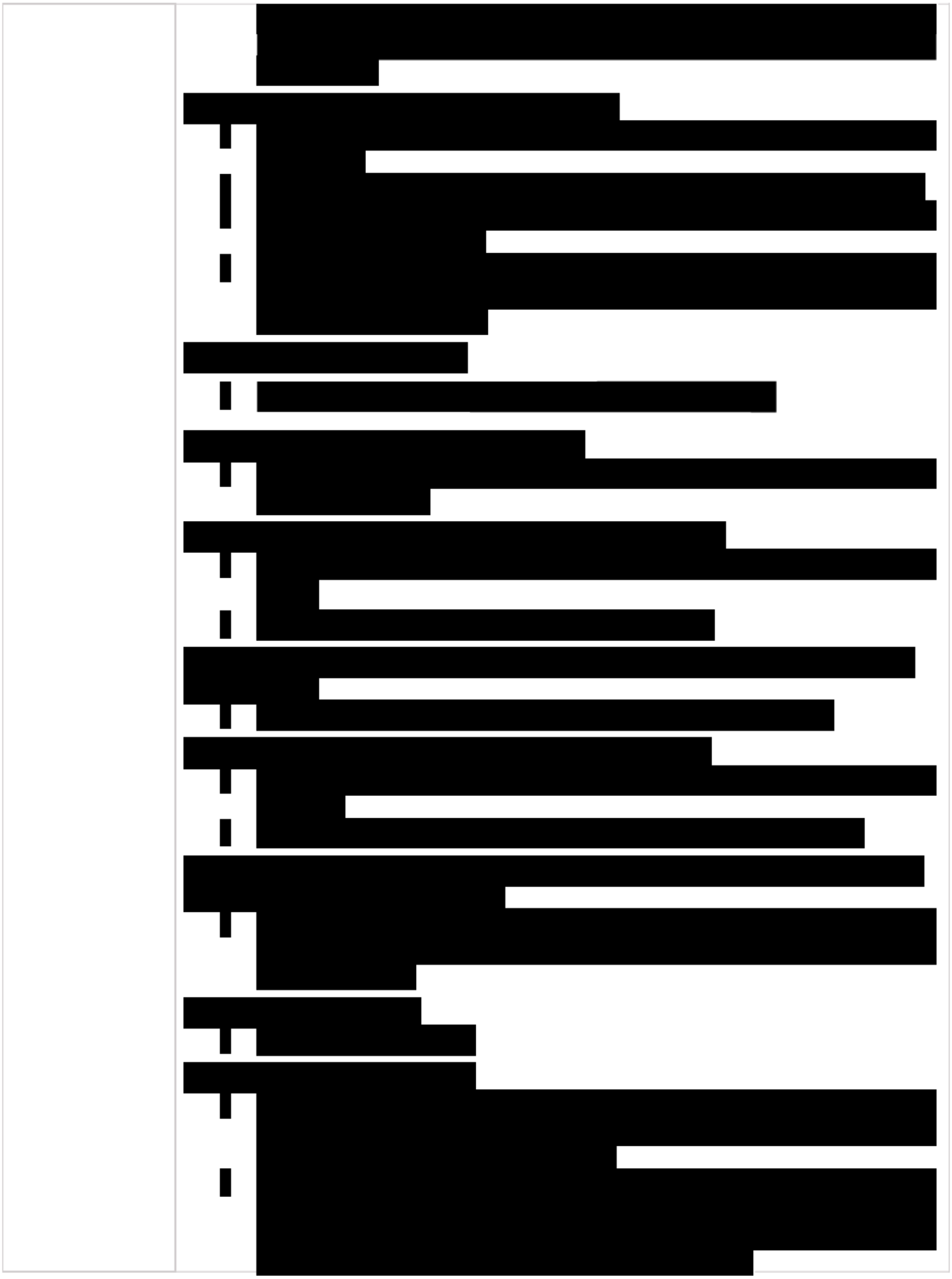
1.0 Approvals

Sponsor	
Sponsor Name:	Harmony Biosciences, LLC
Representative/ Title:	[redacted]
Signature /Date:	
PRA	
Biostatistician / Title:	[redacted] / Senior Principal Statistician
Signature /Date:	

2.0 Change History





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4.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Harmony Biosciences, LLC Protocol HBS-101-CL-002.

5.0 Scope

The SAP outlines the:

- Study Objectives
- Study Design
- Endpoints
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol Amendment 5, Version 6.0 (dated 13 December 2021) and case report form (CRF) Version 4.0 (dated 28 April 2022). Any further changes to the protocol or CRF may necessitate updates to the SAP.

Final approval of the SAP by Harmony Biosciences and by PRA will occur prior to unblinding the Double-Blind Treatment Phase of the study.

6.1 Changes from Protocol

- The Intent-to-Treat Population is renamed as modified Intent-to-Treat (mITT) Population, but the definition remains the same.
- The Pharmacokinetics (PK) Population was revised to include all patients who have at least one non-missing concentration for either analyte. This new definition of the PK Population means that all PK concentrations will be summarized and plotted even for patients with PK concentration available, but for which PK parameters cannot be determined.
- Additional details to resolve convergence issues for the mixed model repeated measures (MMRM) analysis with an unstructured covariance matrix was added.
- For the OLE Phase reporting, all patients will be analyzed under the same treatment group, i.e., patients will not be grouped based on their randomized treatment. During the OLE Phase, patients will undergo a 3-week titration to reach a target dose of 17.8 mg (ages 6 to <12 years), 26.7 mg (ages 12 to <18 years) or 35.6 mg (ages 18 to 65 years) and continue to received pitolisant at that dose (which corresponds to the high pitolisant dose for each age group as defined in the Double-Blind Treatment Phase) unless they were not titrated to the target dose and are receiving a lower dose based on clinical response and/or tolerability; therefore, the randomized treatment group will not influence the results of the OLE Phase.
- Remove the (pooled) site from all inferential models for consistency across analysis/endpoints. Most of the assessments are performed by the caregiver/patient so it is not expected for the site covariate to contribute to the model.

7.0 Study Objectives

7.1 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of pitolisant compared with placebo in treating excessive daytime sleepiness (EDS) in patients with Prader-Willi syndrome (PWS) ages 6 to 65 years.

7.2 Secondary Objectives

Key Secondary Objectives

The key secondary objectives of this study are to evaluate the following in patients with PWS ages 6 to 65 years treated with pitolisant compared with placebo:

- Caregiver-rated impressions of severity of EDS
- Clinician-rated impressions of severity of overall clinical status

Other Secondary Objectives

Other secondary objectives of this study are to evaluate the following in patients with PWS ages 6 to 65 years:

- The impact of pitolisant on behavioral symptoms
- The impact of pitolisant on cognitive function
- Change in caregiver burden
- Safety and effectiveness of pitolisant during long-term treatment

7.3 Exploratory Objectives

The exploratory objectives of this study are to evaluate the following in patients with PWS ages 6 to 65 years:

- The impact of pitolisant on hyperphagia
- The impact of pitolisant on changes in plasma ghrelin levels
- The PK of pitolisant and its major metabolite, BP1.3484
- The relationship between plasma levels of pitolisant (PK) and treatment effect (pharmacodynamics)

8.0 Study Design

8.1 General Design

This is a randomized, double-blind, placebo-controlled, parallel group, Phase 2 proof of concept study in patients (ages 6 to 65 years) with PWS, followed by an optional OLE Phase.

The study will consist of a Screening Period (up to a maximum of 45 days), an 11-week Double-Blind Treatment Phase (including a 3-week Titration Period and an 8-week Stable Dose

Period), and an optional OLE Phase. The OLE Phase is expected to be multi-year in duration. An overall schema of the study design is provided in Figure 1.

During Screening, patients who meet all eligibility criteria will be randomized in a 1:1:1 ratio to receive treatment with low dose pitolisant, high dose pitolisant, or matching placebo (approximately [redacted] patients per treatment group, ages 6 to 65 years). The low and high pitolisant doses, respectively in each age group, will be 8.9 mg and 17.8 mg for children ages 6 to <12 years, 13.35 mg and 26.7 mg for adolescents ages 12 to <18 years, and 17.8 mg and 35.6 mg for adults ages 18 to 65 years.

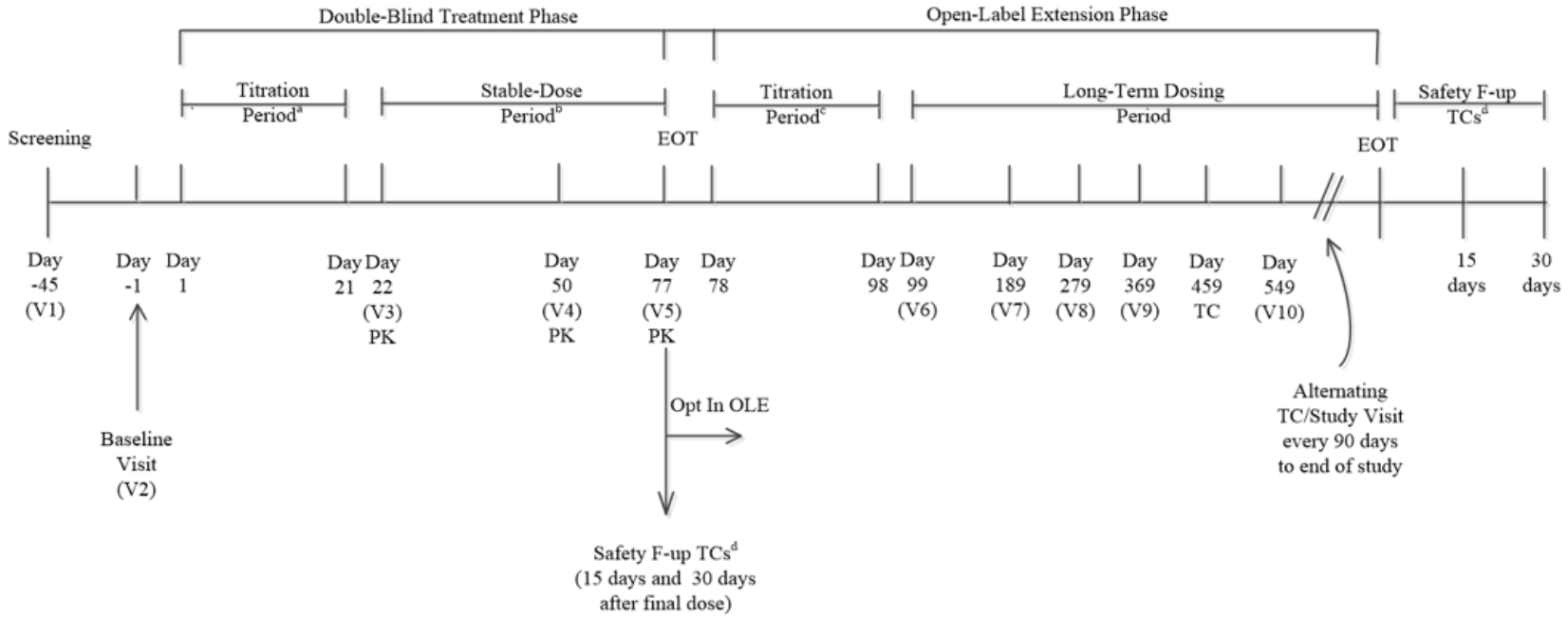
The day after the Baseline Visit, patients will take their first dose of study drug. In the Double-Blind Treatment Phase, patients will be titrated to their randomized stable dose of study drug during the 3-week Titration Period; study drug dose will be titrated on Day 8 and again on Day 15 (based on randomized stable dose, per Table 1, with all patients at their randomized stable dose by Day 15). After completion of the 3-week Titration Period, patients will continue to take study drug at their randomized stable dose for an additional 8 weeks of blinded treatment (Stable Dose Period; Days 22 to 77). The duration of the Double-Blind Treatment Phase will be 11 weeks.

Adjustments to study drug dosing outside the protocol-specified titration schedule are not permitted during the 11-week Double-Blind Treatment Phase of the study.

Eligible patients who complete the Double-Blind Treatment Phase will be given the opportunity to participate in an optional OLE Phase. During the OLE Phase, all eligible patients will complete titration during a 3-week Titration Period to a maximum target dose based on their age (17.8 mg for ages 6 to <12 years, 26.7 mg for ages 12 to <18 years, or 35.6 mg for ages 18 to 65 years; Table 2). At the end of the 3-week Titration Period, patients will continue to take their target dose of pitolisant once daily in the morning upon wakening until the end of the study. Adjustments to pitolisant dose are permitted during the OLE Phase; pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of clinical response, tolerability, and/or patient age. The maximum doses allowed in the study are 17.8 mg for children 6 to <12 years, 26.7 mg for adolescents 12 to <18 years, and 35.6 mg for adults 18 to 65 years.

The Coronavirus Disease 2019 (COVID-19) pandemic has had a major impact on the conduct of clinical trials worldwide, including restrictions on travel, dislocation of clinical trial patients, and the need of many health care facilities to handle an influx of patients with COVID-19. Recognizing the impact of COVID-19 on clinical trials, the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) released guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency. Details of analyses of data collected regarding the impact of COVID-19 on this study are included in applicable sections throughout.

Figure 1: Overall Study Design



Abbreviations: AE = adverse event; EOT = End of Treatment; F-Up =follow-up; OLE = Open Label Extension; PK = pharmacokinetics; TC = telephone call; V = Visit.

[a] The Titration Period for the Double-Blind Treatment Phase will be from Days 1 to 21. Patients will receive their first dose of study drug on Day 1; study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized stable dose); all patients will be at their randomized stable dose by Day 15 of the Titration Period.

[b] The 8-week Stable Dose Period for the Double-Blind Treatment Phase will be from Days 22 to 77 (±3 days); patients will take their last dose of blinded treatment on Day 77 (±3 days). Visit 5 (Day 77 ±3 days) is the EOT Visit for the Double-Blind Treatment Phase. Eligible patients who opt to enter the OLE Phase will be dispensed open-label pitolisant at this visit.

[c] The Titration Period for the OLE Phase will be from Days 78 to 98 (±3 days). Eligible patients will receive their first dose of open-label pitolisant on Day 78 and pitolisant dose will be titrated on Day 85 and again on Day 92 to the target dose. At the end of the 3-week Titration Period, patients will continue to take their target dose of pitolisant once daily in the morning upon wakening until the end of the study (Long-term Dosing Period). During the OLE Phase, pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of clinical response, tolerability and/or patient age; the maximum doses allowed in the study are 17.8 mg for children 6 to <12 years, 26.7 mg for adolescents 12 to <18 years, and 35.6 mg for adults 18 to 65 years.

[d] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient/parent(s)/legal guardian(s) provides written informed consent/assent through 30 days (+3 days) after final dose of study drug (Safety Follow-up TCs). At the Safety Follow-up TCs, AEs (including inquiries regarding

signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded.

During the first year of the OLE Phase of the study, patients will have the option to complete up to two of the scheduled on-site study visits remotely (i.e., two of Visits 6, 7, 8, and 9); thereafter (i.e., after Visit 9/Month 12), patients will have the option to complete one of the two scheduled on-site study visits remotely per year.

Table 1: Study Drug Dosing in the Double-Blind Treatment Phase, Once Daily

Age/Treatment Groups	Titration Period[a] (3 Weeks)			Stable Dose Period[b] (8 Weeks)
	Week 1 (Days 1 – 7)	Week 2 (Days 8 – 14)	Week 3 (Days 15 – 21)	Weeks 4 – 11 (Days 22 – 77)
Pediatric patients (6 to <12 years)				
Low dose pitolisant	4.45 mg	8.9 mg	8.9 mg	8.9 mg
High dose pitolisant	4.45 mg	8.9 mg	17.8 mg	17.8 mg
Placebo	Matching tablets	Matching tablets	Matching tablets	Matching tablets
Adolescent patients (12 to <18 years)				
Low dose pitolisant	4.45 mg	8.9 mg	13.35 mg	13.35 mg
High dose pitolisant	8.9 mg	17.8 mg	26.70 mg	26.70 mg
Placebo	Matching tablets	Matching tablets	Matching tablets	Matching tablets
Adult patients (18 to 65 years)				
Low dose pitolisant	4.45 mg	8.9 mg	17.8 mg	17.8 mg
High dose pitolisant	8.9 mg	17.8 mg	35.6 mg	35.6 mg
Placebo	Matching tablets	Matching tablets	Matching tablets	Matching tablets

[a] Study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized stable dose); all patients will be at their randomized stable dose by Day 15.
[b] Study drug doses for the Stable Dose Period; dose adjustments outside the protocol-specified titration schedule are not permitted in the Double-Blind Treatment Phase.

Table 2: Pitolisant Dosing in the Open-Label Extension Phase, Once Daily

Age Groups	Titration Period[a] (3 Weeks)			Long-Term Dosing Period[b]
	Week 12 Days 78-84	Week 13 Days 85-91	Week 14 Days 92-98	Week 15 (Day 99) to EOT
Pediatric patients (6 to <12 years)	4.45 mg	8.9 mg	17.8 mg	17.8 mg
Adolescent patients (12 to <18 years)	8.9 mg	17.8 mg	26.7 mg	26.7 mg
Adult patients (18 to 65 years)	8.9 mg	17.8 mg	35.6 mg	35.6 mg

Abbreviations: EOT = End of Treatment; OLE = Open-Label Extension
[a] Pitolisant dose will be titrated on Day 85 and again on Day 92.
[b] After completion of the 3-week Titration Period, patients will continue to receive pitolisant at a target dose of 17.8 mg (ages 6 to <12 years), 26.7 mg (ages 12 to <18 years), 35.6 mg (ages 18 to 65 years), unless they were not titrated to the target dose and are receiving a lower dose based on clinical response and/or tolerability.

Note: Adjustments to pitolisant dose are permitted during the OLE Phase. Pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of clinical response, tolerability and/or patient age; the maximum doses allowed in the study are 17.8 mg for children 6 to <12 years, 26.7 mg for adolescents 12 to <18 years, and 35.6 mg for adults 18 to 65 years.

8.2 Sample Size Considerations

The planned sample size is [redacted] patients ([redacted] in the low dose pitolisant group, [redacted] in the high dose pitolisant group, and [redacted] in the placebo group). Prior research suggests that the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) standard deviation (SD) falls between 5 to 6; at the lower end of this range, the study would be powered at [redacted] to detect a difference of [redacted] between the pooled pitolisant dosage groups and placebo group. However, as a proof-of-concept study, statistical separation is not a strict objective of the trial, especially with regard to the individual dosage groups versus placebo. The proposed sample size will yield a 95% confidence interval of [redacted] with an SD of [redacted] and [redacted] with an SD of [redacted]; this will give sufficient precision to inform future studies.

8.3 Randomization

Eligible patients will be randomly assigned in a 1:1:1 ratio via an interactive voice/web response system (IXRS) to low dose pitolisant, high dose pitolisant, or matching placebo.

Enrolled patients will be allocated a unique patient number in a sequential order by trial site. Following randomization, Harmony Biosciences will provide all study drug in a packed and labeled kit, and the IXRS will identify the kit number to be dispensed to the patient at each relevant visit according to the treatment assigned in the randomization schedule.

9.0 Study Endpoints, Conventions and Derivations

9.1 Endpoints

Table 3 and Table 4 list the objectives and the assessments being used for the respective endpoints in the study.

Table 3: Double-Blind Treatment Phase Objectives and Endpoints

DOUBLE-BLIND TREATMENT PHASE	
Primary Objective	**Primary Endpoint**
To evaluate the safety and efficacy of pitolisant compared with placebo in treating EDS in patients with PWS ages 6 to 65 years.	Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo
Key Secondary Objectives	**Key Secondary Endpoints**
To evaluate caregiver-rated impressions of severity of EDS and clinician-rated impressions of severity of overall clinical status in patients with PWS ages 6 to 65 years treated with pitolisant compared with placebo.	Change from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo in: • Caregiver Global Impression of Severity (CaGI-S) for EDS • Clinical Global Impression of Severity (CGI-S) for overall clinical status related to PWS

Other Secondary Objectives	Other Secondary Endpoints
To evaluate the following in patients with PWS ages 6 to 65 years: • The impact of pitolisant on behavioral symptoms • The impact of pitolisant on cognitive function • Change in caregiver burden	Change from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo in: • Behavior as measured by the Aberrant Behavior Checklist, Second Edition (ABC-2) • Behavioral and cognitive rigidity as measured by the Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome (MERS-PWS) • Psychomotor function as measured by the Cogstate Detection test • Attention as measured by the Cogstate Identification test • Working memory as measured by the Cogstate One Back test • Measure of caregiver burden using the 22-item Zarit Burden Interview (ZBI-22)
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the following in patients with PWS ages 6 to 65 years: • The impact of pitolisant on hyperphagia • The impact of pitolisant on changes in ghrelin levels • The PK of pitolisant and its major metabolite, BP1.3484 • The relationship between plasma levels of pitolisant (PK) and treatment effect (PD)	Change from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo in: • Total score of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) in conjunction with the Food Safe Zone Questionnaire (FSZQ) • Acylated and unacylated ghrelin levels PK endpoints for both pitolisant and its major metabolite, BP1.3484: • Maximum observed plasma concentration (C_{max}) • Area under the plasma concentration-time curve (AUC) from time 0 to the last collection time (AUC_{last}) after administration of pitolisant • Time to observed maximum plasma concentration (t_{max}) Exposure-response relationship between plasma pitolisant levels and change in efficacy measures
Safety	**Safety Endpoints**
To assess the safety and tolerability of pitolisant in patients with PWS ages 6 to 65 years	• AEs • Clinical laboratory results • Vital signs • 12-lead electrocardiogram (ECG) • Suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS)

	• Anxiety: Anxiety, Depression, and Mood Scale (ADAMS) • Seizures • Physical Examinations

Abbreviations: ABC-2 = Aberrant Behavior Checklist, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = Adverse Event; AUC = Area under the plasma concentration-time curve; C-SSRS = Columbia-Suicide Severity Rating Scale; CAGI-S = Caregiver Global Impression of Severity; CGI-S = Clinical Global Impression of Severity; C_{max} = Maximum observed plasma concentration; ECG = electrocardiogram; EDS = Excessive Daytime Sleepiness; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; FSZQ = Food Safe Zone Questionnaire; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS- PWS = Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome; PK = Pharmacokinetic(s); PWS = Prader-Willi Syndrome; T_{max} = Time to observed maximum plasma concentration; ZBI-22 = 22-item Zarit Burden Interview.

Table 4: Open-Label Extension Phase Objectives and Endpoints

OPEN-LABEL EXTENSION	
Objectives	**Efficacy Endpoints**
To evaluate the long-term effectiveness of pitolisant	During the patient's first year of participation, changes from Baseline in: • ESS-CHAD as rated by caregivers/parents, • CaGI-S for EDS • CGI-S for overall clinical status related to PWS • ABC-2 • MERS-PWS • Cogstate Detection test • Cogstate Identification test • Cogstate One Back test • ZBI-22 • HQ-CT in conjunction with the FSZQ After the first year of participation, changes from Baseline in: • ESS-CHAD as reported by caregivers/parents • CaGI-S • CGI-S for overall clinical status related to PWS
Safety	**Safety Endpoints**
To assess the safety and tolerability of pitolisant in patient with PWS	• AEs • Clinical laboratory results • Vital signs • 12-lead ECG • Suicidality (C-SSRS)

	• Anxiety (ADAMS) • Seizures • Physical Examinations

Abbreviations: ABC-2 = Aberrant Behavior Checklist, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = Adverse Event; C-SSRS = Columbia-Suicide Severity Rating Scale; CAGI-S = Caregiver Global Impression of Severity; CGI-S = Clinical Global Impression of Severity; ECG = electrocardiogram; EDS = Excessive Daytime Sleepiness; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; FSZQ = Food Safe Zone Questionnaire; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-PWS = Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome; PWS = Prader-Willi Syndrome; ZBI-22 = 22-item Zarit Burden Interview.

9.2 Study Day Windows

For each patient there will be a Screening period, a Double-Blind Treatment Phase, and an OLE Phase (optional).

The study day for data collected prior to first dose, will be calculated as visit date – first dose date. For data collected after the first dose, the study day will be calculated as visit/assessment date – first dose date + 1. The first dose date refers to the date the study drug was taken for the first time, i.e., at the beginning of the Double-Blind Treatment Phase.

9.2.1 Visit Window

The visit window and PK draw window appear in Table 5 and Table 6, respectively. For the Double-Blind Treatment Phase, unless otherwise stated, the endpoints will be analyzed and reported using the analysis visits as determined by the windowing. For the OLE Phase, unless otherwise stated, the nominal visit will be used.

During the Double-Blind Treatment Phase, if a patient stopped taking treatment before their CRF Visit 3 (start of the stable dose) for a reason other than AE and then re-started study treatment more than 14 days after the treatment interruption, the analysis visit window for post-baseline visits will be derived using (as Day 1) the date the patient re-started their study treatment (i.e., the visit window will not be based on date of first dose for that patient).

Table 5: Visit Window and Target Day

Phase	Protocol Visit	Analysis Visit	Target Day	Visit Window Lower Limit	Visit Window Upper Limit
Safety: Vital Signs (including Height and Weight), Physical Examination, Clinical Laboratory, 12-lead ECG **Efficacy: ESS-CHAD (parent/caregiver version), CaGI-S, CGI-S**					
Screening	Visit 1 Visit 2	Baseline	-1	- inf	1
Double-Blind	Visit 3	Visit 3 (Day 22)	22	2	35
	Visit 4	Visit 4 (Day 50)	50	36	63
	Visit 5	Visit 5 (Day 77)	77	64	Treatment Phase Completion[a]
OLE	Visit 6	Visit 6 (Month 4)	99		
	Visit 7	Visit 7 (Month 6)	189		

Phase	Protocol Visit	Analysis Visit	Target Day	Visit Window Lower Limit	Visit Window Upper Limit
	Visit 8	Visit 8 (Month 9)	279		
	Visit 9	Visit 9 (Month 12)	369		
	Visit x	Visit x (Month y)[b]	Previous visit target day + 180		
Efficacy: Ghrelin measurements					
Screening	Visit 2	Baseline	-1	- inf	1
Double-Blind	Visit 5	Visit 5 (Day 77)	77	2	+ inf
Efficacy: Cogstate					
Screening	Visit 1 Visit 2	Baseline	-1	- inf	1
Double-Blind	Visit 4	Visit 4 (Day 50)	50	36	63
	Visit 5	Visit 5 (Day 77)	77	64	Treatment Phase Completion[a]
OLE	Visit 6	Visit 6 (Month 4)[c]	99		
	Visit 7	Visit 7 (Month 6)	189		
	Visit 8	Visit 8 (Month 9)	279		
	Visit 9	Visit 9 (Month 12)	369		
Efficacy: ABC-2, MERS-PWS[c], ZBI-22, HQ-CT and FSZQ					
Screening	Visit 1 Visit 2	Baseline	-1	- inf	1
Double-Blind	Visit 3	Visit 3 (Day 22)	22	2	35
	Visit 4	Visit 4 (Day 50)	50	36	63
	Visit 5	Visit 5 (Day 77)	77	64	Treatment Phase Completion[a]
OLE	Visit 6	Visit 6 (Month 4)	99		
	Visit 7	Visit 7 (Month 6)	189		
	Visit 8	Visit 8 (Month 9)	279		
	Visit 9	Visit 9 (Month 12)	369		
PK					
Double-Blind	Visit 3	Visit 3 (Day 22)	22	2	35
	Visit 4	Visit 4 (Day 50)	50	36	63
	Visit 5	Visit 5 (Day 77)	77	64	+ inf

Abbreviations: ABC-2 = Aberrant Behavior Checklist, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CAGI-S = Caregiver Global Impression of Severity; CGI-S = Clinical Global Impression of Severity; ECG = electrocardiogram; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; FSZQ = Food Safe Zone Questionnaire; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-PWS = Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome; PWS = Prader-Willi Syndrome; ZBI-22 = 22-item Zarit Burden Interview.
Note: For MSLT, C-SSRS and ADAMS no analysis window will be applied; data will be reported using the nominal visit.

[a] In the Double-Blind Treatment Phase, if the patient did not enter the OLE Phase, the upper limit of the visit window should be the date of the end of the completion of the treatment phase as collection in the CRF; if the patient entered the OLE Phase, the upper limit of the visit window should be the first dose of study drug intake in the OLE
[b] Patients will have on-site visits every 6 months (months 18, 24 etc.). Target day is derived by adding 180 days to the previous visit target day.
[c] Not collected at Visit 6 (Month 4) in protocol version 6 and subsequent protocol version(s).

Table 6: PK Draw Timing

Visit	Target Day	
Visit 3	Day 22	Any time after the morning dose of the study drug
Visit 4	Day 50	• Pre-dose • Between 45 and 75 minutes after dosing, • Between 1.5 and 2.5 hours after dosing, • Between 3.0 and 4.0 hours after dosing, • Between 5.0 and 6.0 hours after dosing
Visit 5	77	Any time after the morning dose of the study drug

9.2.2 Data Selection for Multiple Results

Double-Blind Treatment Phase: For post-baseline assessments, if there are multiple non-missing results within the same analysis windows (including scheduled and unscheduled results) the non-missing result that is the closest to the target date will be used in the analyses; if more than one result is equally close, the result that is after the target date for the assessment will be used. If necessary, time of the assessments (if collected) will be used to determine the record to be selected. If there is still more than one result to be selected (but with different results), the average will be derived and then selected for analysis.

OLE Phase: The assessments performed at the nominal visits will be used in the analyses/summaries. Unscheduled assessments will only be used to determine worst, lowest and/or highest results post-baseline (where applicable).

9.3 Baseline

For the Double-Blind Treatment Phase, Baseline is defined as the last record or measure collected prior to the study drug administration. For the OLE Phase, Baseline will be identical to the Double-Blind Treatment Phase, i.e., the last non-missing record or measure collected prior to study drug administration.

9.4 Date of Last Dose

For patients who are lost to follow-up and for which the date of last dose was not known, the date of last dose will be imputed by the date the patient was lost to follow-up, i.e. the date of the Double-Blind Treatment Phase Completion/Discontinuation as collected in the CRF. The imputed date of last dose will be used in the determination of TEAEs, concomitant medications, and duration of exposure.

9.5 Unblinding details (Treatment Received)

After a patient is randomized, IXRS assigns a kit to that patient. Each kit is split into several boxes (one for Week 1, one for Week 2, one for Week 3, one for Week 4 to 7 and one for Week 8 to 11). Each box comprises several bottles of the study drug.

At each visit (Baseline, Visit 3 and Visit 4), the site entered the bottle number (barcode) and the number of tablets in the bottle that was dispensed (and returned). In the event, that the bottle number was not available, the site has been instructed to enter key information (kit ID, week number and type of bottle) to allow the unblinding instead of the bottle number. The kit ID from the integration with

The first step for the unblinding (to determine which treatment received) will be to link the bottle number (when available) with the kit ID using the packaging kit list. In instances where the bottle number is not available (not a numeric value), the kit ID recorded as part of the bottle number information will be used to determine the Kit ID. Once each record from the drug accountability CRF page has been linked to the actual kit ID, the kit list from IXRS will be used to determine the treatment group (low dose pitolisant, high dose pitolisant or placebo).

The actual treatment group for the analysis will be derived as detailed in Section 10.2.

9.6 Double-Blind and OLE Analyses Reporting

The data collected for the Double-Blind Treatment Phase and the OLE Phase are included in the same database.

A CSR will be written at the end of the Double-Blind Treatment Phase and another one at the end of the OLE Phase. The date of first dose in the OLE Phase will be used to determine if the patient entered the OLE Phase.

Double-Blind Treatment Phase:

For reporting of the Double-Blind Treatment Phase analyses, a data cut-off will be applied to the datasets and only data related to the Double-Blind Treatment Phase will be reported, i.e.,

- Baseline and baseline characteristics
- Visits performed in the Double-Blind Treatment Phase, up to and including Visit 5 (Week 11) for patients who entered the OLE Phase and through the safety follow-up visits for patients who opt out of the OLE Phase
- For patients who entered the OLE Phase, any AE or medication that started up to and excluding the first dose of study drug in the OLE Phase.
- For patients who opt out of the OLE Phase, all AEs and medications reported through the final 30-day safety follow-up telephone contact will be reported as part of the Double-Blind Treatment Phase

The date of first dose in the OLE Phase will be kept in the datasets to determine if the patient has entered the OLE Phase.

OLE Phase:

For reporting of the OLE analyses, no data cut-off will be applied to the datasets but only data related to the OLE Phase will be reported, i.e.,

- Demographics and baseline characteristics for patients who received at least one dose of study drug within the OLE Phase
- Baseline of the safety and efficacy data (section 9.3)
- Safety and effectiveness reported during the OLE Phase
- AE and concomitant medications started on or after the 1st dose of OLE study drug intake

10.0 Analysis Sets

For the Double-Blind Treatment Phase: The safety analyses will be conducted on the safety population. The mITT population will be used for efficacy analysis. The PK population will be used for PK analyses. Patients will be analyzed according to randomized treatment assignment for efficacy assessments and according to actual treatment received for safety assessments. Patients will be analyzed by treatment, active arms pooled, and overall (where appropriate).

For the OLE Phase: The Open-Label safety population will be used. After completion of the 3-week Titration Period, patients will continue to receive pitolisant at a target dose of 17.8 mg (ages 6 to <12 years), 26.7 mg (ages 12 to <18 years), 35.6 mg (ages 18 to 65 years), unless they were not titrated to the target dose and are receiving a lower dose based on clinical response and/or tolerability, so all patients will be analyzed under the total treatment group.

10.1 Modified Intent-to-Treat Population

The mITT population will include all randomized patients who received at least one dose of study drug and have one Baseline and at least one post-baseline assessment at any visit of any endpoint during the Double-Blind Treatment Phase. This population will be used to summarize the primary and other efficacy data. Patients will be analyzed according to randomized treatment assignment.

10.2 Double-Blind Safety Population

The Double-Blind safety population will include all patients who are enrolled (i.e., screened) and take at least one dose of double-blind study drug. Patients will be analyzed according to treatment received. In the case of mis-dosing (with the same kit type, e.g. adult kit), patients will be counted at the highest dose they received in the Double-Blind Treatment Phase.

For the patients who have received study drug from a mixture of kit types (e.g. from a child kit and an adolescent kit), the actual treatment will be derived from the treatment group corresponding to the kit(s) associated to their age group (e.g. from the adolescent kit(s) if the patient was an adolescent).

Based on the information in the database and from the reconciliation with the packaging list, 2 patients [redacted] received a mixture of kits and 1 patient [redacted] received 2 bottles (out of 4 bottles) at Visit 4 from an unknown kit (the bottles' number is unknown and cannot be from the assigned kit). Further details for those patients will be included in the CSR.

- Patient [redacted] was dispensed an adolescent IP kit rather than an adult IP kit due to site error with registration in the IXRS. The patient received study drug for week 1 and week2 from the adolescent kit ([redacted]) and starting at week 3 through to week 11, the patient took study drug from an adult kit ([redacted]). For week 1 and week 2 the adolescent and adult kits are identical, therefore there will be no impact on the actual dose received.
- Patient [redacted] received at Visit 4, 2 bottles from a child kit ([redacted]) and 4 bottles from their assigned kit ([redacted]), so for the last 4 weeks of treatment, the patient received either a slightly lower dose than planned or a slightly higher dose than planned, therefore the mis-dosing will have little impact to the actual dose received.

10.3 Open-Label Safety Population

The Open-Label safety population will include all patients who are enrolled in the OLE Phase (i.e., eligible) and take at least one dose of open-label study drug.

10.4 Pharmacokinetic Population

The PK population will include all patients who received at least one dose of study drug and have a non-missing pitolisant PK concentration. Patients will be analyzed by treatment (high dose and low dose), active arms pooled, and overall (placebo patients will be excluded from the PK population).

11.0 Interim Analyses

No interim analysis will be performed.

12.0 Statistical Methods

All analyses will use SAS version 9.4 or higher. The analysis shells for the tables, listings, and figures will be provided in a separate document.

Categorical variables will be summarized using counts and percentages based on the specified population total. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous data will be summarized using non-missing observations (n, mean, SD, median, minimum, and maximum). The median, minimum, and maximum values will be displayed to the same level of the precision as the raw value. Mean and median will be rounded to 1 decimal place greater than the precision of the original value. The SD will be rounded to 2 decimal places greater than the precision of the original value. Confidence intervals, least square (LS) means, and standard error (SE) will be provided as appropriate. Confidence intervals, LS means will present the same precision as the mean value whereas SEs will present the same precision as SD.

P-values will be rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999."

For safety laboratory parameter and ghrelin levels, results reported as "<xx" will be imputed to xx; and result reported as ">xx" will be imputed to xx.

Statistical hypothesis testing will be [redacted] and carried out at the [redacted] level of significance.

The study objective is to evaluate the effectiveness of pitolisant in treating EDS and other symptoms of PWS for the purposes of informing the design of future studies in patients with PWS, a rare pediatric neurodevelopmental disorder. As such, the relative strengths of all measures are of interest and p-values will be reported with no formal multiplicity adjustments.

All the listings will be displayed by treatment arm, patient identifier and date of assessment. Age, sex, and race will be presented.

12.1 Patient Disposition

12.1.1 Disposition

When the Double-Blind Treatment Phase is complete, the number and percentage of patients screened, randomized, randomized and treated, randomized and not treated, completed the Double-Blind Treatment Phase, discontinued from the Double-Blind Treatment Phase, and eligible to enter in the OLE Phase will be summarized, together with a breakdown of the corresponding reasons for discontinuation from study drug and from the study. The number and percentage of patients included in each analysis set will be summarized as well.

The number of patients who screen failed and the reason for screening failure will be tabulated. A supportive data listing will be provided for the screening failure patients and will include the reason for screen failure and the list of inclusion/exclusion criteria failed.

For the OLE Phase, the number and percentage of patients who were treated in the OLE Phase, who completed or discontinued from the OLE Phase, and who discontinued from study drug in the OLE Phase along with the associated reasons for discontinuation from the study drug and/or the OLE Phase will be summarized.

Patient disposition data will be presented in a data listing for Double-Blind safety and Open-Label safety.

12.1.2 Important Protocol Deviations

All protocol deviations identified during monitoring or from data cleaning are recorded in the clinical trial management systems. However, deviations pertaining to unblinding information (i.e., a patient has received the incorrect kit and did not receive the treatment they were randomized to) will be programmatically derived. Those deviations will be deemed important deviations relating to study drug.

Based on all treated patients, the number and percentage of patients with important protocol deviations by category will be summarized by treatment arm, active arms pooled, and overall for the Double-Blind Treatment Phase and overall for the OLE Phase.

Important protocol deviations will be listed, and all COVID-19-related protocol deviations will be listed separately.

12.1.3 Inclusion and Exclusion Criteria

Failed inclusion and exclusion criteria for randomized patients will be presented in a data listing.

12.2 Demographic and Baseline Characteristics

12.2.1 Demographics

Baseline data will be summarized for continuous and categorical variables as applicable.

The following demographic and baseline characteristics will be summarized:

- Sex (female, male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age (years) at Baseline, as continuous variable and Age groups (6 to 11 years; 12 to <18 years, ≥ 18 years)
- Height at Baseline (m)
- Weight at Baseline (kg)
- Body mass index at Baseline (kg/m^2) defined as Weight (kg)/[Height (m)]^2
- Women of child-bearing potential
- Patients with/without concomitant sleep disorders (or sleep disorder symptoms) that could potentially contribute to EDS beyond the EDS associated with PWS. Medical terms that are specifically used to describe EDS (e.g., hypersomnia, hypersomnolence, sleepiness, etc.) will not be used to infer a concomitant sleep disorder or sleep disorder symptom as EDS is required for study entry.

At the time of the Double-Blind Treatment Phase database lock, the above information will be tabulated by treatment arm, active arms pooled and overall, using the mITT, PK and the Double-Blind safety populations. At the time of OLE Phase database lock, the above information will be tabulated using the Open-Label safety population.

Data will not be re-collected at entry to the OLE Phase but will be reported for the subset of patients who enter the OLE Phase.

Demographic information will be presented in a data listing. No statistical testing will be performed on the demographic data.

12.2.2 Medical History

A complete medical history will be obtained at Screening to ensure patients qualify for the study and will be updated at the Baseline visit if needed.

Medical history will be summarized for all patients in the safety populations. Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The version used will be included in the tables and listings footnotes and summarized by system organ class and preferred term. No inferential testing will be performed in this section. Medical history data will be presented in a data listing.

12.2.3 Seizure History

Seizure history will be obtained at Screening and will be updated at the Baseline visit if needed.

For all patients in the safety population, in those patients with a history of a seizure disorder, the following aspects of their seizure history will be summarized.

- Has there been any change in seizure activity in the past 3 months (prior to the study)?
- Type of seizure disorder
- Average weekly seizure frequency
- Average seizure duration in seconds

No inferential testing will be performed in this section. Seizure history data will be presented in a data listing.

12.2.4 Prader-Willi Syndrome History

Confirmation of a patient's diagnosis of PWS will be obtained via review of the patient's medical records. Age at diagnosis of PWS and the type of PWS will be tabulated.

- Age at diagnosis of PWS (years) = (date of diagnosis – date of birth)/365.25
- Type of PWS

The date of diagnosis of PWS and the type of PWS will be presented in a data listing. If the date of diagnosis is partial, the date will be imputed as:

- If only the day is missing it will be imputed as the 15th day of the month
- If the day and month are missing, they will be imputed as 15th of July

12.3 Treatments

12.3.1 Prior, Concomitant and Prohibited Medications

Medications that stop prior to the first dose of study drug will be classified as prior medications. Medications that start on or after the first dose of study drug will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug (or is ongoing), then the medication will be classified as both prior and concomitant.

Medications will be categorized by medication group and subgroup according to World Health Organization (WHO) drug dictionary (the version used will be included in the tables and listings footnotes).

Missing or partial medication start/stop date will be imputed as described in Appendix 2. A conservative approach will be used when flagging medications.

Prior and concomitant medications will be summarized by preferred name and medication class. Frequency count and percentage of patients using each medication along with the number and percentage of patients using at least one medication within each medication and medication class will be presented. All medications will be listed.

For patients who opt to continue in the OLE Phase of the study, only medications starting strictly before the first dose in the OLE Phase will be summarized for the Double-Blind Treatment Phase, and any medications that started on or after the first dose of treatment in the OLE Phase and up to 30 days after the last dose of treatment in the Double-Blind Treatment Phase will be included in a

separate listing (for the OLE Phase reporting); these medications will be included in the OLE Phase summaries.

12.3.1.1 Prohibited and Restricted Concomitant Medications

The use of medications that may prolong the QT interval is not permitted in the study.

Use of opiates is not permitted in the study.

Except for diazoxide choline, use of investigational drugs (i.e., drugs that are not FDA-approved for any indication) are prohibited.

The use of strong CYP2D6 inhibitors or strong CYP3A4 inducers is not permitted during the Double-Blind Treatment Phase of the study, and if being used, should be discontinued at Screening; washout of 5 half-lives or 1 week (whichever is longer) of these medications is required prior to enrollment and initiating study drug. These medications (Appendix 3) are allowed during the OLE Phase of the study, but adjustment of the dose of pitolisant may be required.

Pitolisant increases the levels of histamine in the brain; therefore, centrally acting histamine 1 (H_1) receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of pitolisant. Concomitant use of centrally acting H_1 receptor antagonists is not permitted during the Double-Blind Treatment Phase of the study (requires a washout of 5 half-lives or 14 days, whichever is longer, prior to randomization). Although not prohibited during the OLE Phase of the study, use of these medications should be avoided and, if needed, will require consultation with the Medical Monitor.

Prohibited medications taken in the study will be reported and summarized as part of the protocol deviations summary/listing.

12.3.2 Extent of Study Drug Exposure

Descriptive statistics will be provided by treatment group for the Double-Blind Treatment Phase analyses and by treatment group received, active arms pooled, and overall, during the Double-Blind Treatment Phase and overall, for the OLE Phase analyses.

12.3.2.1 Double-Blind Treatment Phase

The duration of exposure to study drug, number of days with intake of study drug and compliance (during the stable dose period) with study drug dosing will be summarized for the Double-Blind safety population. In addition, the number of tablets taken (i.e., returned – dispensed) will be listed for the titration phase and the stable dose phase in the Double-Blind Treatment Phase.

Study drug accountability including bottle number and number of dispensed and returned tablets will be listed. Study drug not returned will be assumed to have been taken.

Percentage of patients meeting study drug compliance during the stable-dose period will be presented in the following categories: <80%, ≥80% to ≤120%, and >120%. Major non-compliance is defined as compliance <80% or compliance >120%.

Duration of exposure: Date of last dose in the Double-Blind Treatment Phase – date of first dose in the Double-Blind Treatment Phase + 1

Number of days with at least one dose (tablet) taken: Duration of exposure in the Double-Blind Treatment Phase – number of days with missed doses in the Double-Blind Treatment Phase

Study drug compliance (stable-dose period): The start date of the stable dose period is the date of Visit 3 (Day 22) and the end of the stable dose period is the last dose date in the Double-Blind Treatment Phase; during that period patients ages 6 to <12 years should take 4 tablets daily, patients ages 12 to <18 years should take 6 tablets daily, and patients ages ≥18 years should take 2 tablets daily; i.e., compliance is the number of tablets taken during that period (i.e., sum of the tablets dispensed minus the sum of the tablets returned) divided by (x times the number of days in the period [date of last dose – dispensed date at Visit 3 +1]), where x is 4 for patients ages 6 to <12 years, 6 for patients ages 12 to <18 years and 2 for patients ages ≥18 years.

The data from the dose-escalation period was not included in the derivation of the compliance as the dates when the patient dose-escalated to the next dose level is not collected in the eCRF and the number of tablets to be taken at each dose level is different.

There is one patient [redacted] who had their last dose date recorded in the CRF ([redacted]) before the drug was dispensed at Visit 3 ([redacted]), which is the start of the stable dose period; the bottles were returned to the site, but 4 tablets were missing. As confirmed via queries to the site, those tablets were not taken and the date of last dose is correct. In such instance where the compliance cannot be calculated (date of last dose before the date drug dispensed at Visit 3), the compliance will not be derived.

12.3.2.2 OLE Phase

The duration of exposure to study drug will be summarized for the Open-Label safety population. Study drug accountability and number of dispensed and returned tablets will be listed.

Duration of exposure: Date of first dose in the OLE Phase – date of last dose in the OLE Phase + 1

In addition, the following measures of changes in planned dose will be summarized for the Open-Label safety population:

- Planned average daily dose: sum of the daily dose x duration of intake (end date minus start date + 1) divided by the duration of exposure
- Number and percentage of patients with at least one dose adjustment per reason (AE, dosing error, rechallenge, insufficient effectiveness, change in dose assignment criteria and other)
- Number and percentage of patients with one dose adjustment, with two dose adjustments and with >2 dose adjustments due to any reason
- Number and percentage of patients with one dose adjustment, with two dose adjustments and with >2 dose adjustments due to AE
- Number and percentage of patients with one dose adjustment, with two dose adjustments and with >2 dose adjustments due to rechallenge
- Number and percentage of patients with one dose adjustment, with two dose adjustments and with >2 dose adjustments due to insufficient effectiveness

12.4 Efficacy Analyses

12.4.1 Double-Blind Treatment Phase

All efficacy analyses will be performed on the mITT Population. Results of the Double-Blind Treatment Phase will be reported following database lock once all patients have completed or discontinued the Double-Blind Treatment Phase of the study.

12.4.1.1 Hypothesis Testing Strategy

The study is a Phase 2 proof of concept and is not powered to show statistical significance; therefore, no formal multiplicity adjustment will be done.

All tests will be 2-sided. P-values will be reported for the individual doses, the combined doses, and for all the outcomes.

The following order reflects the endpoints of most interest and greater consideration will be given to successful endpoints higher in the list, particularly when all preceding endpoints have a significant p-value. For the secondary endpoints, interpretation of the results regarding statistical significance will be based on the pattern of results.

Primary Endpoint:

- Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5) for the high dose group compared with placebo
- Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5) for the low dose group compared with placebo
- Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5) for the pooled active doses group compared with placebo

Key Secondary Endpoints:

- Change from Baseline to Week 11 (Visit 5) in Caregiver Global Impression of Severity (CaGI-S) for EDS for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Clinician Global Impression of Severity (CGI-S) for overall clinical status related to PWS for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in CaGI-S for EDS for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in CGI-S for overall clinical status related to PWS for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in CaGI-S for EDS for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in CGI-S for overall clinical status related to PWS for the pooled active doses group compared with placebo

Other Secondary Endpoints:

- Change from Baseline to Week 11 (Visit 5) in behavior as measured by the Aberrant Behavior Checklist, Second Edition (ABC-2) for the high dose group compared with placebo

- Change from Baseline to Week 11 (Visit 5) in behavioral and cognitive rigidity as measured by the Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome (MERS-PWS) for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Psychomotor function as measured by the Cogstate Detection test for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Attention as measured by the Cogstate Identification test for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Working memory as measured by the Cogstate One Back test for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Measure of caregiver burden using the 22-item Zarit Burden Interview (ZBI-22) for the high dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in behavior as measured by the ABC-2 for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in behavioral and cognitive rigidity as measured by the MERS- PWS for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Psychomotor function as measured by the Cogstate Detection test for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Attention as measured by the Cogstate Identification test for the low dose doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Working memory as measured by the Cogstate One Back test for the low dose group compared with placebo
- Change from Baseline to Week 11(Visit 5) in Measure of caregiver burden using the ZBI-22 for the low dose group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in behavior as measured by the ABC-2 for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in behavioral and cognitive rigidity as measured by the MERS- PWS for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Psychomotor function as measured by the Cogstate Detection test for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Attention as measured by the Cogstate Identification test for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Working memory as measured by the Cogstate One Back test for the pooled active doses group compared with placebo
- Change from Baseline to Week 11 (Visit 5) in Measure of caregiver burden using the ZBI-22 for the pooled active doses group compared with placebo

12.4.1.2 Missing Data Imputations

No explicit imputation will be performed for the primary analysis; however, the MMRM model will yield unbiased results under the assumption that data are missing at random.

A sensitivity analysis for the primary endpoint (change from Baseline in mean ESS-CHAD [parent/caregiver version] score) will be performed using a hypothetical strategy. In this approach,

the unobserved data following discontinuation for lack of efficacy or AEs will be assumed to follow the placebo distribution at the matching visit, conditioned on the patient's observed data (including Baseline). Missing data after a patient discontinues treatment (for reasons other than lack of efficacy and AE) and intermittent missing data will be assumed to be missing at random. Details for the imputation are provided in this section.

Patients who discontinue early from the Double-Blind Treatment Phase study drug will be asked to return to the clinic for an Early Termination (ET) visit for completion of assessments (schedule of assessments in Appendix 7). The ESS-CHAD (parent/caregiver version) score collected at ET visit will be mapped to be closest analysis visit based on the rules defined in section 9.2. A multiple imputation approach will be utilized for missing data at Visit 3 (Day 22), Visit 4 (Day 50) and Visit 5 (Day 77, Week 11).

Table 7 represents the imputation rules for the primary endpoint sensitivity analysis. Missing data will be imputed using a three-stage multiple imputation (MI) approach.

Table 7: Post-Baseline Values Scenario and Imputation Methods

Study Medication Status	Analysis Visit			Imputation
	Visit 3	Visit 4	Visit 5	
Completed/ Discontinued	Present	Missing	Present	Intermittent missing data will be imputed within treatment group using MI under a missing at random assumption with observed values at all available time points (including Baseline).
	Missing	Present	Present	
	Missing	Missing	Present	
Discontinued due to lack of efficacy or due to AE	Present	Present	Missing	Missing data after the discontinuation will be imputed within the Placebo group (regardless of their assigned treatment group) using MI approach with observed values at all available time points (including Baseline).
	Present	Missing	Missing	
	Missing	Missing	Missing	
Discontinued due to any reason but lack of efficacy or AE	Present	Present	Missing	Missing data after the discontinuation will be imputed within treatment group using MI approach with observed values at all available time points (including Baseline).
	Present	Missing	Missing	
	Missing	Missing	Missing	

Abbreviations: AE = Adverse Event; MI = Multiple Imputation.

Note: Multiple imputation method is performed using the analysis visits, i.e., if the nominal result is missing, and there is an unscheduled result or if the ET result falls within the visit window that assessment will be used at that visit.

Step 1. Monotone Missing Pattern: Intermittent missing data will be imputed within treatment group using MI under a missing at random assumption with observed values at all available time points (including Baseline).

a. From the analysis dataset containing the ESS-CHAD (parent/caregiver version) results, select all the patients (regardless of the discontinuation reason and status). The dataset will contain indicators variables for subject ID: SUBJID, planned treatment: TRTP, Baseline results: BASELINE, Visit 3 results: VISIT3, Visit 4 results: VISIT4 and Visit 5 results: VISIT5) and there will be one record per patient. Before transposing the dataset to get the required structure, if there are multiple non-missing records for a patient, select the record to include as per the rules defined in section 9.2.

b. Using this dataset with treatment as covariate, [redacted] imputed datasets (called imputations) will be produced using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure. The imputed datasets will contain the observed value (where it was not originally missing) or imputed values as per the model (for missing observations). The values imputed by MCMC method for the missing values will be used for patients who completed the treatment phase but have monotone patterns of missing data.

Step 2. Missing data for patients who discontinued for other reasons (i.e., not due to lack of efficacy or AE): Missing data after the treatment discontinuation (i.e., in the 'tail' end) will be imputed within treatment group distribution (intermittent missing data will have been imputed at the previous step). Patients who completed the treatment but have missing values not imputed at the previous step (i.e., at the 'tail' end) will have their missing imputed together with patients who discontinued for other reasons.

a. Using the dataset created in step 1, select all the patients regardless of the discontinuation status and reason for discontinuation.

b. Using this dataset, one imputation will be produced using the MCMC method implemented with the SAS MI procedure. The values imputed by MCMC method for the missing values will be used for patients who discontinued treatment for reason other than lack of efficacy or AE.

Step 3. Missing data for patients who discontinued due to lack of efficacy or AE: Missing data after the treatment discontinuation will be imputed using the placebo group distribution, regardless of their assigned treatment group. The control-based pattern imputation will be implemented by breaking the imputation process into a sequence of multiple calls to PROC MI, where each call is intended to impute missing values at one time-point only, so the sequence will be repeated for each visit (Visit 3, Visit 4 and Visit 5).

a. From the dataset created in step 2 and for the patients who discontinued due to lack of efficacy or AE, set to missing the results that occurred after the last visit performed for those patients (the last visit performed corresponds to the last analysis visit with no missing data prior to imputation).

b. Split the dataset into 2 datasets:

   - Dataset 1 includes all the patients in the placebo group (regardless of the discontinuation reason and status) as well as all the patients in the other treatment

groups (low dose pitolisant and high dose pitolisant) who discontinued treatment before Visit 3 due to lack of efficacy or AE.

- Dataset 2: includes all the other patients.

c. Using this dataset, one imputation will be produced using a monotone regression controlled for Visit 3 implemented with the SAS MI procedure (variables order will be Baseline and Visit 3). Once the imputation has been performed all patients who discontinued treatment due to lack of efficacy or AE in the active group will have Visit 3 data imputed.

d. The dataset generated by the MI procedure (step 3c) will be appended to the dataset 2 (step 2b). This dataset will include all the patients.

e. The previous steps (b to d) are repeated for each visit (Visit 4 and Visit 5).

The datasets created by the MI procedures at each of the above steps will include 20 records (imputations) per patient for each visit, the changes from Baseline will be derived to obtained Visit 3 change from Baseline, Visit 4 change from Baseline and Visit 5 change from Baseline values. The dataset (created at the last step) will be transposed back to have a record per patient and visit and will include the variables to support the sensitivity analysis.

The following options will be used when using the MI procedure:

- For step 1 and step 2, the input datasets for the MI procedure will be sorted by planned treatment group (numeric) and patient. For step 3, the input datasets for the MI procedure will be sorted by patient.
- For step 1 and step 2, the order of the variables in the MI procedure will be Baseline, Visit 3, Visit 4 and Visit 5; a statement by treatment will be included in the procedure.
- For step 3, the order of the variables in the MI procedure will be Baseline, Visit 3 (for all iterations), Visit 4 (from the second iteration) and Visit 5 (for the last iteration).
- The number of imputations will be [redacted] (nimpute=[redacted]) for the step 1 and will be [redacted] imputation (nimpute=[redacted]) for the steps 2 and 3.
- The data sampling will be rounding the number of decimal point available in the raw data.
- The option min and max will be used to force the procedure to resample, so the values fall within the observed/collected values. For the imputations described in step 2, the minimum and maximum values will be set to the minimum and maximum values of all observed data within the considered parameter collected within the Double-Blind Treatment Phase for the randomized patients (regardless of visits and treatment group).
- For step 1, monotone imputation will be selected with chain as multiple for the MCMC imputation.
- For step 2, the MCMC imputation, single chain (chain=single) with full imputation (imputation=full) will be used. There will be [redacted] burn-in iterations before the first imputation in each chain (nbiter=[redacted]) and [redacted] iterations between imputations in a single chain (niter=[redacted]). Finally, Jeffreys prior (specifies a non-informative prior) will be used (prior=Jeffreys). Upon review of the plots that will be produced by the MCMC statement,

the burn-in iterations before the first imputation in each chain (nbiter) can be increased to [redacted] if required.

If the algorithm described in one of the steps (or sub-step) cannot be implemented due to insufficient data, the step will be skipped.

The seeds defined in Table 8 will be used to reproduce the proc MI results. Examples of code are provided in Appendix 4.

Table 8: Sensitivity Analysis Primary Endpoint Multiple Imputation Seeds

Endpoint	Step 1	Step 2	Step 3
ESS-CHAD (parent/caregiver version)	121897	121898	121918 (1st iteration), 221918 (2nd iteration) 321918 (3rd iteration)

Abbreviation: ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents.

12.4.1.3 Primary Efficacy Analysis

12.4.1.3.1 Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) [parent/caregiver version]

The primary endpoint is change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5).

The parent/caregiver version of the ESS-CHAD is an [redacted] Likert rating scale where parents/caregivers rate their child's/care recipient's likelihood of falling asleep over the past month while engaging in eight different activities. If the patient has not engaged in an activity, the parent/caregiver is asked to imagine how the activity would have affected the patient. Responses are rated on a scale where [redacted]. A global score, which represents the sum of responses across all eight items, ranges from [redacted]; higher scores correspond to greater daytime sleepiness. If one or more item-scores are missing, the score will be missing.

The score can be interpreted as:

12.4.1.3.2 Estimand

The primary efficacy endpoint is defined as the change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 (Visit 5) for high dose pitolisant compared with placebo.

The target population is all patients in the mITT population with PWS as defined by the inclusion/exclusion criteria.

A treatment policy strategy will be used to address intercurrent events. No special data handling will be used for patients who initiate concomitant medications, have intermittent missing data, or discontinue study medication (even if they report data following discontinuation of study medication). No explicit imputation of missing data will be performed; the MMRM approach assumes data are missing at random and will provide unbiased results if this is the case. Sensitivity analyses will explore the results under different analysis assumptions.

12.4.1.3.3 Analysis

A descriptive summary (mean, SD, median, minimum, maximum) of the mean ESS-CHAD (parent/caregiver version) score (absolute values and change from Baseline) will be reported by treatment group and for the active groups combined. Early Termination visits will be summarized under Visit 3, Visit 4 or Visit 5 (depending on which visit they are closest to, per section 9.2) regardless of the discontinuation reason.

Frequency count and percentage of the ESS-CHAD (parent/caregiver version) score category ([redacted]); at each visit versus Baseline category will be provided by way of shift tables. In addition, the frequency count and percentage of the ESS-CHAD (parent/caregiver version) responder (improvement of [redacted] points from Baseline or a score which is less or equal to [redacted]) will be tabulated by treatment group and active groups combined. Percentages will be based on the number of patients with non-missing ESS-CHAD (parent/caregiver version) at Baseline and at each post-baseline visit. Patients with a score at Baseline which is less or equals [redacted], will not be included in the summary.

No explicit imputation will be performed for the primary analysis; however, the MMRM model will yield unbiased results under the assumption that data are missing at random.

The change from Baseline will be analyzed in an MMRM analysis. Fixed effects will be included for treatment, Baseline value, visit and a term for the interaction between treatment and visit. An unstructured covariance structure will be utilized; Kenward-Rogers degrees of freedom will be used.

In the case of convergence issues, the following steps will be implemented (in the order listed) until convergence is reached.

1. The Fisher scoring algorithm will be used to start the first iteration to obtain the initial values of the covariate parameters (via the SCORING option of the PROC MIXED statement).
2. The no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T is the total number of time points), which effectively performs the Cholesky decomposition of the covariance matrix and is numerically more stable.
3. The successive univariate regression (Lu 2010) will be implemented.
4. Covariance matrix of ARH(1) (Heterogeneous auto-regressive 1), and CS (compound symmetry) with the sandwich variance estimator will be used in that order (for the sandwich variance estimator Kenward-Rogers degrees of freedom will be replaced by the EMPIRICAL option).

LS means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts. The primary comparison of interest is the difference in the high dose group versus placebo at Visit 5.

Examples of SAS code are provided in Appendix 4.

12.4.1.3.4 Sensitivity Analysis

A sensitivity analysis will be performed using a hypothetical strategy. In this approach, the unobserved data following discontinuation for lack of efficacy or AEs will be assumed to follow the placebo distribution at the matching visit, conditioned on the patient's observed data (including Baseline). Patients who discontinue for all other reasons and intermittent missing data will be assumed to be missing at random.

The change from Baseline will be analyzed in an MMRM model run on each of the [redacted] MI replicates obtained as per the process described in section 12.4.1.2 and combined using Mianalyze (Rubin 1976). Fixed effects will be included for treatment, Baseline value, visit and a term for the interaction between treatment and visit. An unstructured covariance structure will be utilized; in the case of convergence issues, the same approaches as defined in section 12.4.1.4.3 will be followed; Kenward-Rogers degrees of freedom will be used. LS means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts.

12.4.1.4 Key Secondary Efficacy Analyses

Descriptive summary of each of the secondary endpoints will be provided (mean, SD, median, minimum, maximum) for the absolute values and change from Baseline. All summaries will be presented by treatment group and for the active groups combined.

12.4.1.4.1 Caregiver Global Impression of Severity (CaGI-S)

CaGI-S for EDS is a [redacted] Likert rating scale completed by the parent/caregiver to assess the likelihood of the patient falling asleep during daytime activities [redacted], with the following possible responses:

[redacted]

Early Termination visits will be summarized under Visit 3, Visit 4, or Visit 5 (depending on the visit they are closest to, per section 9.2) regardless of the discontinuation reason.

Frequency count and percentage of patients for each category and by visit will be provided as well as shift from Baseline. In addition, the number and percentage of patients with at least one-point improvement from Baseline (responder) will be summarized by treatment group and active groups combined. Percentages will be based on the number of patients with non-missing CaGI-S at Baseline and at each post-baseline visit.

The change from Baseline will be analyzed using a MMRM approach. Fixed effects will be included for treatment, visit, treatment*visit interaction and, Baseline value. An unstructured covariance structure will be utilized; in the case of convergence issues, the same approaches as defined in section 12.4.1.4.3 will be followed; Kenward-Rogers degrees of freedom will be used. LS means, SE, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts.

12.4.1.4.2 Clinical Global Impression of Severity (CGI-S)

From protocol version 1 to protocol version 3, CGI-S for overall impression of severity was a [redacted] Likert-type rating scale completed by the investigator to assess the patient's condition, with the following possible responses:

From protocol version 4, CGI-S for overall impression of severity is a [redacted] Likert-type rating scale completed by the investigator to assess the patient's condition, with the following possible responses:

For the reporting results from the [redacted] Likert-type rating scale will be mapped to the [redacted] Likert-type rating scale as shown in Table 9.

Table 9: Mapping from [redacted] Likert-type Rating Scale to [redacted] Likert-type Rating Scale

[redacted] Likert-type Rating	[redacted] Likert-type Rating
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The same summaries and analysis as performed for CaGI-S will be repeated for the CGI-S endpoint. Further details on the inferential analysis are provided in section 12.4.1.5.1.

In addition, the number and percentage of patients with at least one-point improvement from Baseline (responder) will be summarized by treatment group and active groups combined. Percentages will be based on the number of patients with non-missing CGI-S at Baseline and at each post-baseline visit.

12.4.1.5 Other Secondary Efficacy Analyses

Descriptive summary of each of the other secondary endpoints will be provided (mean, SD, median, minimum, maximum) for the absolute values and change from Baseline. All summaries will be presented by treatment group and for the active groups combined.

The other secondary efficacy endpoints are change from Baseline to Week 11 (Visit 5) in the following:

- Behavior as measured by the ABC-2
- Behavioral and cognitive rigidity as measured by the MERS-PWS
- Psychomotor function as measured by the Cogstate Detection test
- Attention as measured by the Cogstate Identification test
- Working memory as measured by the Cogstate One Back test
- Measure of caregiver burden using the ZBI-22

12.4.1.5.1 Aberrant Behavior Checklist, Second Edition (ABC-2)

The ABC-2 assesses problematic behavior at home, in educational and work settings, and in residential and community-based facilities. The checklist rates 58 specific symptoms and provides comprehensive descriptions for each assessed behavior, divided into five subscales (there is no total score):

- Irritability (15 items)
- Social withdrawal (16 items)
- Stereotypic behavior (7 items)
- Hyperactive/non-compliance (16 items)
- Inappropriate speech (4 items)

The ABC-2 will be completed by the patient's caregiver who will score the items on a [redacted] Likert scale ranging from [redacted] to [redacted].

The scores from each item are summed in each subscale as shown in Table 10. For a score to be calculated, the number of missing items should be 3 or less for the irritability scale, social withdrawal scale and hyperactivity/non-compliance scale, 2 or less for the stereotypic behavior scale, and 1 or less for the inappropriate speech scale.

The score for each scale will be derived by 1) adding the score for the non-missing items, 2) dividing the sum obtained by the number of items answered and 3) multiplying by the number of items in the scale.

Table 10: ABC-2 Sub-Scales Scoring

Sub-scale	Items #
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The irritability score ranges from [redacted], the social withdrawal score ranges from [redacted], the stereotypic behavior score ranges from [redacted], the hyperactivity/non-compliance score ranges from [redacted] and the inappropriate speech score ranges from [redacted].

The same analysis as performed for CaGI-S will be repeated for the each of the ABC-2 subscales. Further details on the inferential analysis are provided in section 12.4.1.5.1.

12.4.1.5.2 Montefiore-Einstein Rigidity Scale-Prader-Willi Syndrome (MERS-PWS)

The MERS-PWS is a clinician-rated, semi-structured interview conducted with both the patient with PWS and caregiver present. The MERS-PWS measures the following three domains of rigid behavior:

- **Behavioral Rigidity Domain**: difficulty managing behavior in new, unfamiliar, or unexpected situations (e.g., insistence on sameness, things must be done in his/her way, difficulty when a change interrupts plans/activity, etc.)
- **Cognitive Rigidity Domain:** lack of flexible thinking (e.g., repetitive/perseverative questioning in response to lack of flexible thinking, need to know or check for reassurance, difficulty shifting "gears" and/or conversation topics)
- **Protest Domain:** the behavioral response (i.e., protest) that results from a real or perceived interruption to rigidity (i.e., severity of protest [irritability, verbal objections, tantrums, nonresponsive, etc.], length of protest, interference due to protest, and the effort needed to calm the patient down from the protest)

Within each domain, [redacted] items are rated on a scale of [redacted], the scores for each domain are added, and [redacted] composite scores are calculated ([redacted]). The domains and composite scores are calculated as shown in Table 11. If one or multiple items are missing (not answered), the corresponding domain score and composite score(s) will not be calculated.

Table 11: Scoring Rules for MERS-PWS

Domains/Composites	Sum of the following items
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The behavior rigidity score ranges from [redacted], the cognitive rigidity score ranges from [redacted], the protest score ranges from [redacted], the total rigidity composite score ranges from [redacted] and the total domains composite score ranges from [redacted]. A higher score reflects more rigid behavior.

The same analysis as performed for CaGI-S will be repeated for the each of the MERS-PWS domains and composites scores. Further details on the inferential analysis are provided in section 12.4.1.5.1.

12.4.1.5.3 Cogstate Detection Test

The Cogstate Detection test is a computerized measure of psychomotor function and uses a validated simple reaction time (RT) paradigm with playing card-like stimuli displayed on a computer screen. [redacted]. The main outcome measure for the test is speed of performance (mean of the $\log_{10}$-transformed RTs for correct responses). Decreasing scores represent improved test performance.

Early Termination visits will be mapped to the closest planned visit (section 9.2) regardless of the discontinuation reason.

The change from Baseline will be analyzed with an MMRM approach. Fixed effects will be included for treatment, visit, treatment*visit interaction and Baseline value. An unstructured covariance structure will be utilized; Kenward-Rogers degrees of freedom will be used.LS means, SE, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts. Significance tests will be based on LS means using a [redacted]. The effect size (magnitude of the differences between treatment groups and placebo) will also be provided.

The analysis of the Detection test will be performed by Cogstate: more details are provided in the Cogstate SAP.

12.4.1.5.4 Cogstate Identification Test

The Cogstate Identification test is a computerized measure of visual attention and uses a validated choice RT paradigm with playing card-like stimuli displayed on a computer screen. In this test, [redacted] The main outcome measure for the test is speed of performance (mean of the log_{10}-transformed RTs for correct responses). Decreasing scores represent improved test performance.

Early Termination visits will be mapped to the closest planned visit (section 9.2) regardless of the discontinuation reason.

The same analyses as performed for Cogstate Detection test will be repeated for the Cogstate Identification test endpoint. Further details on the inferential analyses are provided in section 12.4.1.6.3.

12.4.1.5.5 Cogstate One Back Test

The Cogstate One Back Test is a computerized measure of working memory and uses a validated n-back paradigm with playing card stimuli displayed on a screen. [redacted] Decreasing scores represent improved test performance.

Early termination visits will be mapped to the closest planned visit (section 9.2) regardless of the discontinuation reason.

The same analyses as performed for Cogstate Detection test will be repeated for the Cogstate One Back test endpoint. Further details on the inferential analyses are provided in section 12.4.1.6.3.

12.4.1.5.6 22-Items Zarit Burden Interview (ZBI-22)

The ZBI-22 is a self-reported questionnaire in which caregivers are asked to rate their experience on a [redacted] Likert scale ([redacted]) for 22 questions related to caregiver health and psychological well-being, finances, impact on social life, and relationship with the individual with the disability. Responses are summed to derive the ZBI-22 total score ([redacted]), where higher scores represent greater burden.

If more than [redacted] items out of [redacted] are missing, the score will be set to missing. Otherwise, the score will be derived by 1) adding the non-missing items, 2) dividing the sum obtained by the number of items answered and 3) multiplying by 22.

The same analysis as performed for CaGI-S will be repeated for the ZBI-22 total score. Further details on the inferential analysis are provided in section 12.4.1.5.1.

12.4.1.6 Exploratory Efficacy Analyses

Other exploratory efficacy endpoints include change from Baseline to Week 11 (Visit 5) in each of the following:

- Total score of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) in conjunction with the Food Safe Zone Questionnaire (FSZQ)
- Acylated and unacylated ghrelin levels
- Exposure-response relationship between plasma pitolisant concentrations and changes in efficacy measures
- Psychomotor/Attention Composite Score
- Psychomotor/Attention/Working Memory Composite Score

12.4.1.6.1 Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

The HQ-CT is a [redacted] questionnaire designed to measure food-related preoccupations and problems in PWS, as well as the severity of these concerns. The questionnaire is an observer-reported outcome measure, completed by caregivers who report on the patient's hyperphagic symptoms. Higher scores are related to increased hyperphagia. The HQ-CT is used in conjunction with the FSZQ, which assesses the level of food environmental control required for patients.

The HQ-CT total score is derived by summing the [redacted] item-level responses, yielding a score ranging from [redacted]; the computation of an HQ-CT total score requires responses to at least six items, and any missing responses (up to [redacted]) are replaced with the average of the remaining (completed) item responses.

The same analysis as performed for CaGI-S will be repeated for the HQ-CT total score. Further details on the inferential analysis are provided in section 12.4.1.5.1.

12.4.1.6.2 Food Safe Zone Questionnaire (FSZQ)

The FSZQ is a [redacted] observer-reported measure of environmental controls that are in place to manage hyperphagia in patients with PWS. The FSZQ is performed in conjunction with the HQ-CT. [redacted]
Caregivers will complete this assessment. Higher scores are associated with higher levels of environmental food control, and as patients with PWS respond favorably to treatment, scores are expected to decrease as the level of control over their food environment lessens. If one or more item-scores are missing, the score will be missing.

The same analysis as performed for CaGI-S will be repeated for the FSZQ total score. Further details on the inferential analysis are provided in section 12.4.1.5.1.

12.4.1.6.3 Serum Ghrelin Levels

Samples for serum ghrelin levels (acylated and unacylated) will be collected while the patient is fasting and may be collected at the same time as sample collection for clinical laboratory tests.

The change from Baseline will be analyzed in an ANCOVA model. Fixed effects will be included for treatment and Baseline value. LS means, SE, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will

be generated from a single model, i.e., the pooled estimates will be created via model contrasts. Significance tests will be based on LS means using a [redacted]

12.4.1.6.4 Multiple Sleep Latency Test (MSLT)

The multiple sleep latency test (MSLT) is not collected starting with the protocol version 6, therefore only a summary table and listing will be provided.

MSLT is a standard tool that tests for EDS by measuring how quickly a patient falls asleep in a quiet environment during the day. The MSLT is a full-day test [redacted]

The mean of the sleep latency will be derived using the sleep latency obtained from [redacted]; only valid assessments will be considered. The assessment from a nap will be deemed valid if the duration of the sleep time for that nap is [redacted]. Nap [redacted] will be excluded from the average as it is assumed the results from the last naps will be overinflated. If there is only one valid nap, the average will not be derived and therefore will not be included in the summary table.

The mean of the sleep latency and its change from Baseline will be summarized (for the data collected) and listed.

12.4.1.6.5 Subgroup Analysis

Subgroups analysis for each age group (6 to <12 years; 12 to <18 years and 18 years or older) will be conducted for the following endpoints:

- Change in mean score from Baseline in ESS-CHAD (parent/caregiver version) at Visit 3, Visit 4 and Visit 5
- Change from Baseline in CaGI-S at Visit 3, Visit 4 and Visit 5
- Change from Baseline in CGI-S at Visit 3, Visit 4 and Visit 5
- Change from baseline in HQ-CT at Visit 3, Visit 4 and Visit 5
- Change from Baseline in acylated ghrelin levels at Visit 5
- Change from Baseline in unacylated ghrelin levels at Visit 5

Subgroups analysis for patients with/without concomitant sleep disorders that could potentially contribute to EDS beyond the EDS associated with PWS, and sleep disorder symptoms will be conducted for the following endpoints. Medical terms that are specifically used to describe EDS (e.g., hypersomnia, hypersomnolence, sleepiness, etc.) will not be used to infer a concomitant sleep disorder or sleep disorder symptom as EDS is required for study entry.

A manual review of the medical history for each patient will be performed by a blinded medically trained person(s) to determine which patients have sleep disorders, or comorbidity(es) associated with sleep disorder(s) that may contribute to EDS, apart from medical terms that are specifically used to describe EDS (e.g., hypersomnia, hypersomnolence, sleepiness, etc.). The final

determination and approval by Harmony Biosciences will be conducted on clean data and prior to unblinding of the Double-Blind Treatment Phase.

- Change in mean score from Baseline in ESS-CHAD (parent/caregiver version) at Visit 3, Visit 4 and Visit 5
- Change from Baseline in CaGI-S at Visit 3, Visit 4 and Visit 5
- Change from Baseline in CGI-S at Visit 3, Visit 4 and Visit 5

Summary for actuals and change from Baseline by treatment groups (low dose, high dose, pooled active doses and placebo) will be provided for each endpoint and subgroup.

Inferential statistics will be derived if the sample size in each subgroup is strictly greater than [redacted] The MMRM approach with fixed effects of Baseline value, visit and a term for the interaction between treatment and visit will be implemented. An unstructured covariance structure will be utilized; Kenward-Rogers degrees of freedom will be used.

In the case of convergence issues, the following steps will be implemented (in the order listed) until convergence is reached.

1. The Fisher scoring algorithm will be used to start the first iteration to obtain the initial values of the covariate parameters (via the SCORING option of the PROC MIXED statement).
2. The no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T is the total number of time points).
3. Covariance matrix of ARH(1) (Heterogeneous auto-regressive 1), and CS (compound symmetry) with the sandwich variance estimator will be used in that order (for the sandwich variance estimator Kenward-Rogers degrees of freedom will be replaced by the EMPIRICAL option).

The MMRM will be replaced with an ANCOVA (with treatment and Baseline as fixed effect) or a simple t-test if sample size does not permit more complicated modeling approaches within a subgroup (i.e., in case of convergence issues, or the difference in the change from Baseline cannot be estimated).

12.4.1.6.6 Exposure-response relationship between plasma pitolisant concentrations and changes in efficacy measures

The following plots will be produced to evaluate to exposure-response between the plasma pitolisant concentrations and change in efficacy measures. Only the plots with sufficient data will be produced (e.g., [redacted]).

- Panel plot of mean plasma pitolisant concentration over time (linear and semi-logarithmic scales) by ESS-CHAD (parent/caregiver version) responder status at Visit 5 (responder and non-responder), treatment group (low dose, high dose and pooled active doses) and/or age groups. Patients with no post-baseline ESS-CHAD (parent/caregiver version) will not be included in the plots.
- Panel plot of mean plasma pitolisant concentration over time (linear and semi-logarithmic scales) by CaGI-S categories (no improvement or worsening vs. improvement at Visit 5),

treatment group (low dose, high dose and pooled active doses) and/or age groups. Patients with no CaGI-S assessment at Visit 5 will not be included in the plots.

- Panel plot of mean plasma pitolisant concentration over time (linear and semi-logarithmic scales) by CGI-S categories (no improvement or worsening vs. improvement at Visit 5), treatment group (low dose, high dose and pooled active doses) and/or age groups. Patients with no CGI-S assessment at Visit 5 will not be included in the plots.
- Further plots and analysis of relationship between plasma pitolisant concentrations and change in efficacy measures may be investigated.

12.4.1.6.7 Cogstate Psychomotor/Attention Composite Score and Psychomotor/Attention/ Working Memory Composite Score

The Cogstate Psychomotor/Attention Composite Score will be derived from Cogstate Detection test and Cogstate Identification test by standardizing the test scores against the performance score of the study sample at Baseline. If z-scores are available (i.e., non-missing) for both tests, then they will be averaged to compute the Psychomotor/Attention Composite Score.

Similarly, the Cogstate Psychomotor/Attention/Working Memory Composite Score will be derived from Cogstate Detection test, Cogstate Identification test and One Back test by standardizing the test scores against the performance score of the study sample at Baseline. If z-scores are available (i.e., non-missing) for all three tests, then they will be averaged to compute the Psychomotor/Attention/Working Memory Composite Score.

The same analyses as performed for cogstate Detection test will be repeated for the each of the composite score. Further details on the inferential analyses are provided in section 12.4.1.6.3.

12.4.2 Open-Label Extension Effectiveness Analyses

Actual and change from Baseline results collected in the OLE Phase will be tabulated with summary statistics for continuous outcomes and frequencies and percentages for categorical outcomes. No p-values will be reported for the OLE Phase. Results will be tabulated for the total group. Baseline will be the pre-double-blind-treatment Baseline (identical to that used for the double-blind analyses).

The following endpoints will be summarized for OLE:

- ESS-CHAD score as rated by caregivers/parents
- CaGI-S for EDS
- CGI-S for overall clinical status related to PWS
- Behavior as measured by the ABC-2
- Behavioral and cognitive rigidity as measured by MERS-PWS
- Psychomotor function as measured by the Cogstate Detection test
- Attention as measured by the Cogstate Identification test
- Working memory as measured by the Cogstate One Back test
- Measure of caregiver burden using ZBI-22
- Total score of the HQ-CT in conjunction with the FSZQ
- Cogstate Psychomotor/Attention Composite Score
- Cogstate Psychomotor/Attention/Working Memory Composite Score

The following endpoints will only be collected for the first year of the OLE study (i.e., at Visit 6 [Month 4], Visit 7 [Month 6], Visit 8 [Month 9] and Visit 9 [Month 12]):

- Behavior as measured by the ABC-2
- Behavioral and cognitive rigidity as measured by MERS-PWS
- Psychomotor function as measured by the Cogstate Detection test
- Attention as measured by the Cogstate Identification test
- Working memory as measured by the Cogstate One Back test
- Measure of caregiver burden using ZBI-22
- Total score of the HQ-CT in conjunction with the FSZQ
- Cogstate Psychomotor/Attention Composite Score
- Cogstate Psychomotor/Attention/Working Memory Composite Score

The following endpoints will be collected until the end of the study:

- ESS-CHAD score as rated by caregivers/parents
- CaGI-S for EDS
- CGI-S for overall clinical status related to PWS

In addition, the same categorical summaries provided for the Double-Blind Treatment Phase will be provided for:

- ESS-CHAD score as rated by caregivers/parents
- CaGI-S for EDS
- CGI-S for overall clinical status related to PWS

12.5 PK Analyses

Plasma concentration-time data of pitolisant and BP1.3484 will be summarized using descriptive statistics by age group (6 to <12 years; 12 to <18 years, ≥18 years), treatment group, and scheduled sampling interval. The following summary statistics will be included for plasma concentration-time data: mean, SD, coefficient of variation (CV%), geometric mean, geometric SD, median, minimum, and maximum.

Plasma concentration-time profiles of pitolisant and BP1.3484 will be plotted on semi-log and linear scales for each individual patient as spaghetti plots by age group (6 to <12 years; 12 to <18 years, ≥18 years) and treatment group using actual collection times. For ease of presentation, mean plasma concentration-time data of pitolisant and BP1.3484 will be plotted separately by midpoint (on hour scale) for the planned interval on both linear and semi-logarithmic scales. Plasma PK concentrations of pitolisant and BP1.3484 for each individual will be reported to the precision of the raw data in listing presentations. In addition, concentration-time profiles for each analyte will be plotted by patient.

Values reported as below the lower limit of quantification (LLOQ) or below the limit of quantification (BLQ) i.e., reported as <LLOQ (BLQ) will be imputed to be 0.

If data allow, the following steady-state PK parameters will be calculated for each analyte as listed in Table 12.

Table 12: PK Parameters

Parameter	Description	PK Analysis Notes	Analyte	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.		Pitolisant and BP1.3484	Cmax from WinNonLin software (WNL) version 8.1.1 or later.
T_{max}	Time to reach C_{max} in plasma. The time to reach maximum concentration is obtained directly from the experimental data without interpolation and expressed in time units.		Pitolisant and BP1.3484	Tmax from WNL
$AUC_{(0-T)}$	Area under the concentration-time curve from time 0 (dosing) to the time of the last quantifiable concentration observed, without interpolation or extrapolation, using trapezoidal summation. $AUC_{(0-T)}$ is expressed in concentration*time units.	Calculated by the linear up/log down method in WNL	Pitolisant and BP1.3484	AUClast from WNL
$AUC_{(tau)}$	Area under the {plasma / serum} concentration-time curve over the sampling interval (time 0 to XXhr) using trapezoidal summation. The actual duration of tau is used to capture this parameter. To capture AUC_{tau}, the actual time deviation should be <10%.	Calculated by the linear up/log down method in WNL	Pitolisant and BP1.3484	AUC from WNL summary file at corresponding mid-point XX Flag to List only if: Percent difference in planned and actual sampling at tau ≥10%
C_{max}/D	Dose normalized maximum plasma concentration.		Pitolisant	Cmax / dose

Parameter	Description	PK Analysis Notes	Analyte	SAS Programming Notes
$AUC_{(0-T)}/D$	Dose normalized area under the concentration-time curve from time 0 (dosing) to the time of the last quantifiable concentration observed.	Calculated by the linear up/log down method in WNL	Pitolisant	AUClast / dose
C_{trough}	Observed plasma concentration immediately prior to dose.		Pitolisant and BP1.3484	Predose concentration (Day 22, 50, 77)

PK parameters will be summarized overall and by treatment group and age. The following summary statistics will be included for plasma concentration-time data: mean, SD, CV%, geometric mean, geometric SD, median, minimum, and maximum. Only the median, minimum, and maximum will be calculated for t_{max}.

The plasma concentration-time data from this study may be combined with data from previous studies that utilized the same bioanalytical method, and population PK analyses may be conducted as post hoc analysis; results will be provided in a separate report.

12.6 Safety Analyses

All safety analyses will be completed for the Double-Blind safety and Open-Label safety populations. All safety data will be listed and summarized. No formal statistics will be performed for the safety analysis.

For the Double-Blind Treatment Phase, summaries will be presented by treatment arms and active arms pooled; for the OLE Phase, results will be tabulated for the overall group.

12.6.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure and up to 30 days after the last dose of study drug. For the OLE Phase, any AE starting on or after the first dose of OLE treatment will be considered treatment emergent.

A serious AE (SAE) is defined as any AE that results in any of the following outcomes: death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected in eCRF: definitely related, probably related, possibly related,

unlikely related, or not related. The AEs that are evaluated as definitely, probably, or possibly related (or with missing relationship) will be considered treatment-related AEs for summary purposes.

The severity of AEs will be classified by the investigator as mild, moderate, or severe. If the severity is missing, the AE will be assumed to be severe.

An overall AE summary will be generated presenting the frequency and percentage of patients and the number of AEs for the following categories. This overall summary will also be provided for each age groups (6 to <12 years; 12 to <18 years and 18 years or older) for the Double-Blind Treatment Phase. The same summary may be repeated for the OLE Phase.

- Any TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any treatment-related severe TEAE
- Any serious TEAE
- Any treatment-related serious TEAE
- Any TEAE leading to study discontinuation
- Any TEAE leading to discontinuation of investigational product (IP)
- Any TEAE leading to discontinuation of IP and leading to study discontinuation
- Any TEAE leading to interruption of IP
- Any TEAE leading to death

All AEs will be coded using MedDRA; the version used will be included in the tables and listings footnotes. The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), and (where applicable) by severity.

The TEAE summary tables will be sorted by SOC and PT. SOCs will be displayed in descending order of overall frequency and then alphabetically. PTs will be displayed in descending order of overall frequency and then alphabetically within SOC. A patient with 2 or more events within the same SOC or PT will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of patients in the safety population.

The following summaries by SOC and PT will be provided:

- TEAE
- Treatment-related TEAE
- TEAE by maximum severity
- Serious TEAE
- Treatment-related serious TEAE
- TEAE leading to discontinuation of IP

- TEAE leading to interruption of IP
- TEAE leading to death

In addition, all AEs and all SAEs (regardless of treatment-emergent status) will be tabulated by SOC and PT.

Finally, the following summaries by SOC and PT will be provided for each age groups (6 to <12 years; 12 to <18 years and 18 years or older) for the Double-Blind Treatment Phase. The same summaries by age groups may be repeated for the OLE Phase.

- TEAE
- Treatment-related TEAE
- TEAE by maximum severity

All AEs will be presented in a data listing. Separate data listings will be generated for treatment related AEs, SAEs, AEs leading to death and AEs leading to study discontinuation.

For patients who opt to continue in the OLE Phase of the study, only AEs starting strictly before the first dose in the OLE Phase will be summarized for the Double-Blind Treatment Phase, and any AEs that started on or after the first dose of treatment in the OLE Phase and up to 30 days after the last dose of treatment in the Double-Blind Treatment Phase will be included in a separate listing (for the OLE Phase reporting); these AEs will be included in the OLE Phase summaries. A listing of all the AEs that were ongoing (i.e. that are ongoing or have a stop date after the first dose of treatment in the OLE Phase) at the end of the Double-Blind Treatment Phase will be included in the OLE Phase reporting to capture additional information for those AEs (such as end date and potential treatments) and patients will not necessarily be on the same treatment as what they were randomized to in the Double-Blind Treatment Phase.

For the OLE Phase, the same data summaries and listings will be produced. The data will be tabulated for overall and by period [redacted]. Calculations for AE start and stop dates are detailed in Appendix 5 .

12.6.2 Seizure Disorder

In patients with a history of seizure disorders, the worsening of seizures or change in seizure type will be reported as AEs and the type, duration, and frequency of occurrence will be recorded in the CRF. Patients who experience worsening of their seizure disorder should be withdrawn from the study.

A summary table of seizure activity will be sorted by SOC and PT. All seizures will be presented in a data listing.

12.6.3 Clinical Laboratory Evaluations

Laboratory parameters to be collected are listed in Appendix 6 will be summarized for the Double-Blind safety population and the Open-Label safety population. Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to International System of Units (SI) for reporting and processing purposes. Absolute values and changes from Baseline will be presented descriptively.

Hematology, serum chemistry, and urinalysis will be summarized using descriptive statistics for numeric variables and numbers and percentages for categorical variables at each scheduled assessment. Numeric hematology, chemistry, and urinalysis results will be summarized using change from Baseline as well. Where it is applicable to categorize a laboratory assessment by Normal, High, or Low according to the normal range provided by the central laboratory, the lowest and highest post-baseline results will be compared with that at the study Baseline and the "shifts" from study Baseline will be summarized using the number and percentage of patients in each shift category by treatment group. The shift tables (for hematology and biochemistry) will also be provided for each of age groups (6 to <12 years; 12 to <18 years and 18 years or older) for the Double-Blind Treatment Phase. The same summaries by age groups may be repeated for the OLE Phase.

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Pregnancy tests and urine drug screen will be listed only.

12.6.4 Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, weight, body temperature and height. Patients will be resting for at least [redacted] minutes before taking vital signs.

Vital sign results and corresponding change from study Baseline values will be summarized at each scheduled visit using descriptive statistics by treatment group for Double-Blind safety population and Open-Label safety population.

All vital sign, body weight, and height measurements will be presented in a data listing.

Table 13 includes the normal ranges for the parameter of interest. Frequency count and percentage of patients with low/high vital signs will be tabulated at each visit and by treatment group. Shift from Baseline will also be provided. Results outside of the normal ranges will be flagged in the data listing. As the ranges are dependent on age, in the OLE, age will be derived at each visit. Those summaries by normal ranges will also be provided for each of age groups (6 to <12 years; 12 to <18 years and 18 years or older) for the Double-Blind Treatment Phase. The same summaries by age groups may be repeated for the OLE Phase.

Table 13: Vital Signs Normal Ranges by Age Group

Parameter	Low	High	Normal
Children (6-12 years)			
Systolic Blood Pressure (mmHg)	< 80	> 120	80 – 120
Diastolic Blood Pressure (mmHg)	< 55	> 70	55 – 70
Heart Rate (beat per minutes)	< 70	> 110	70 – 110
Respiration Rate (breath per minutes)	< 20	> 30	20 – 30
Temperature (°C)	<35.5	>37.5	35.5 – 37.5

Parameter	Low	High	Normal
Weight (kg)	< 20	> 42	20 – 42
Adolescent (13-17 years)			
Systolic Blood Pressure (mmHg)	< 110	> 120	110 – 120
Diastolic Blood Pressure (mmHg)	< 57	>71	57 – 71
Heart Rate (beat per minutes)	< 55	> 105	55 – 105
Respiration Rate (breath per minutes)	< 12	> 20	12 – 20
Temperature (°C)	<36.3	>37.3	36.3 – 37.3
Weight (kg)	< 50		≥ 50
Adults (≥ 18 years)			
Systolic Blood Pressure (mmHg)	< 80	> 130	80 – 130
Diastolic Blood Pressure (mmHg)	< 60	> 90	60 – 90
Heart Rate (beat per minutes)	< 60	> 100	60 – 100
Respiration Rate (breath per minutes)	< 12	> 20	12 -20
Temperature (°C)	< 36.6	> 37.3	36.6 – 37.3

12.6.5 Physical Examinations

Full physical examinations will include an evaluation of the head and neck as well as cardiovascular, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems (Appendix 7 and Appendix 8). Abbreviated physical examinations will be performed based on patient/caregiver-reported symptoms (Appendix 7 and Appendix 8).

All physical examination results will be presented in a data listing.

12.6.6 Electrocardiograms

Triplicate 12-lead electrocardiogram (ECG) will be obtained after the patient has been resting for at least 5 minutes. For clinically significant ECG findings, a follow-up ECG should be performed within 24 hours and again 7 days later to ensure the abnormality is not worsening. Follow-up 12-lead ECGs may be performed locally, with the results sent to the Investigator.

Heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB interval, QTcF interval as well as investigator's interpretation of the ECG will be collected in the eCRF. All ECG results along with the investigator's interpretation, including the average of triplicate measurements at each timepoint, will be presented in data listings.

QTcF values will be presented with the implementation of corrections (i.e., Fridericia's) as defined in International Council for Harmonisation (ICH) Guidelines E14. Frequency count and percentage will be tabulated by the following categories. This summary will also be provided for each of age groups (6 to <10 years; 10 to <20 years and 20 to ≤65 years) and sex for the Double-Blind Treatment Phase. The same summaries by age groups and/or sex may be repeated for the OLE Phase.

Absolute QT interval corrected for heart rate based on Fridericia's formula (QTcF) prolongation:

- QTcF interval >442 ms (6 to <10 years old)
- QTcF interval >439 ms (10 to <20 years old)
- QTcF interval >450 ms (male, 20 to ≤65 years)
- QTcF interval >470 ms (female, 20 to ≤65 years)
- QTcF interval >500 ms (regardless of age and gender)

Change from Baseline in QTcF interval:

- QTcF interval increases from Baseline 30-60 ms
- QTcF interval increases from Baseline >60 ms

In addition, potential QT prolongations will be categorized as:

- PR interval >300 msec
- QRS duration >140 msec
- PR interval increase from Baseline >50%
- QRS duration increase from Baseline >40%
- HR increase >65% from Baseline
- HR decrease >40% from Baseline

The actual values and change from Baseline values at each time point will be summarized for the safety populations. The overall interpretation will also be summarized by timepoint as well as the worst post-baseline.

12.6.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) scale is composed of [redacted] items answered [redacted]. The C-SSRS also includes a suicidal ideation intensity rating from [redacted]

Results of C-SSRS will be provided in listings only.

12.6.8 Anxiety, Depression, And Mood Scale (ADAMS)

Anxiety, Depression, and Mood Scale (ADAMS), is a [redacted] designed to assess mood and anxiety symptoms; each item is scored from [redacted]. As shown in Table 14, the [redacted] questions are split into [redacted] domains (some questions are assigned to more than one domain); domain scores are then obtained by summing the response to each question. If an item has not been scored, the corresponding domain score(s) will not be derived. Higher scores indicate a more severe problem or a more frequent behavior.

Table 14: Scoring for each Domain

Manic/ Hyperactive Behavior	Depressed Mood	Social Avoidance	General Anxiety	Obsessive/ Compulsive Behavior
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results of ADAMS and change from Baseline will be summarized at each nominal visit and provided in data listings. This summary will also be provided for each of age groups (6 to <12 years; 12 to <18 years and 18 years or older) for the Double-Blind Treatment Phase. The same summary by age group may be repeated for the OLE Phase.

The following data will also be summarized (from the Baseline assessment):

- Background of the individual being rated:
  - Level of intellectual disability
  - Living situation
  - Disabilities
- Information for the individual completing the form:
  - Relationship with the individual
  - Length of relationship
  - Setting of contact

13.0 References

Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14(6):540-5.

Rubin D. B. Inference and Missing Data. Biometrika. 1976; 63:581-92.

SAS Institute Inc. 2015. SAS 9.4 Procedures Guide. 5th ed. Cary, NC: SAS Institute Inc.

Lu K. and Mehrotra D.V. Specification of covariance structure in longitudinal data analysis for randomized clinical trials. Statistics in Medicine 2010 Feb 20; 29(4):474-88.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ABC-2	Aberrant Behavior Checklist, Second Edition
ADAMS	Anxiety, Depression, and Mood Scale
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration-time curve
AUC_{last}	AUC from time 0 to the last collection time
BLQ	Below the limit of quantification
CaGI-S	Caregiver Global Impression of Severity
CGI-S	Clinical Global Impression of Severity
CHW	Cui, Hung, Wang
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram, electrocardiography
EDS	Excessive daytime sleepiness
EOT	End of Treatment
ESS-CHAD	Epworth Sleepiness Scale for Children and Adolescents
ET	Early Termination
FDA	Food and Drug Administration
FSZQ	Food Safe Zone Questionnaire
GCP	Good Clinical Practice
H_1	Histamine 1
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
ICH	International Council for Harmonisation
inf	infinity
IXRS	Interactive voice/web response system
LLOQ	Lower limit of quantification
LS	Least square

MERS-PWS	Montefiore-Einstein Rigidity Scale – Prader-Willi Syndrome
MI	Multiple Imputations
mITT	Modified Intent-to-Treat
MMRM	Mixed effect model repeated measures
MSL	Mean sleep latency
MSLT	Multiple sleep latency test
NIH	National Institutes of Health
OLE	Open-Label Extension
PK	Pharmacokinetic(s)
PSG	Polysomnography
PWS	Prader-Willi syndrome
QTcF	QT interval corrected for heart rate based on Fridericia's formula
RT	Reaction time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard Error
SI	International System of Units
TEAE	Treatment-emergent adverse event
t_{max}	Time to observed maximum plasma concentration
US	United States (of America)
WHO	World Health Organization
WNL	WinNonLin software
ZBI-22	22-item Zarit Burden Interview

Appendix 2 Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 3 Example of Prohibited Medications

Examples of medications that are strong CYP2D6 inhibitors, strong CYP3A4 inducers, medications that prolong QT interval, and centrally acting H_1 receptor antagonists.

Medication Type	Example
Strong CYP2D6 inhibitors	paroxetine, fluoxetine, bupropion, metoclopramide, and quinidine.
Strong CYP3A4 inducers	rifampin, carbamazepine, phenytoin, dexamethasone, ethosuximide, griseofulvin, primidone, progesterone, rifabutin, nafcillin, nelfinavir, nevirapine, phenobarbital, phenylbutazone, St John's wort, sulfadimidine, sulfinpyrazone, and troglitazone
Medications that prolong QT interval	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: moxifloxacin
H_1 receptor antagonists	pheniramine maleate, diphenhydramine, promethazine (anti-histamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants
Opiates	
Investigational drugs (with the exception of diazoxide choline)	

CYP = cytochrome P450.

Note: Although Section 5.7.1 of the protocol mentions carbetocin and oxytocin as being permitted, they were in fact prohibited due to being investigational drugs (Section 5.7.2 in the protocol).

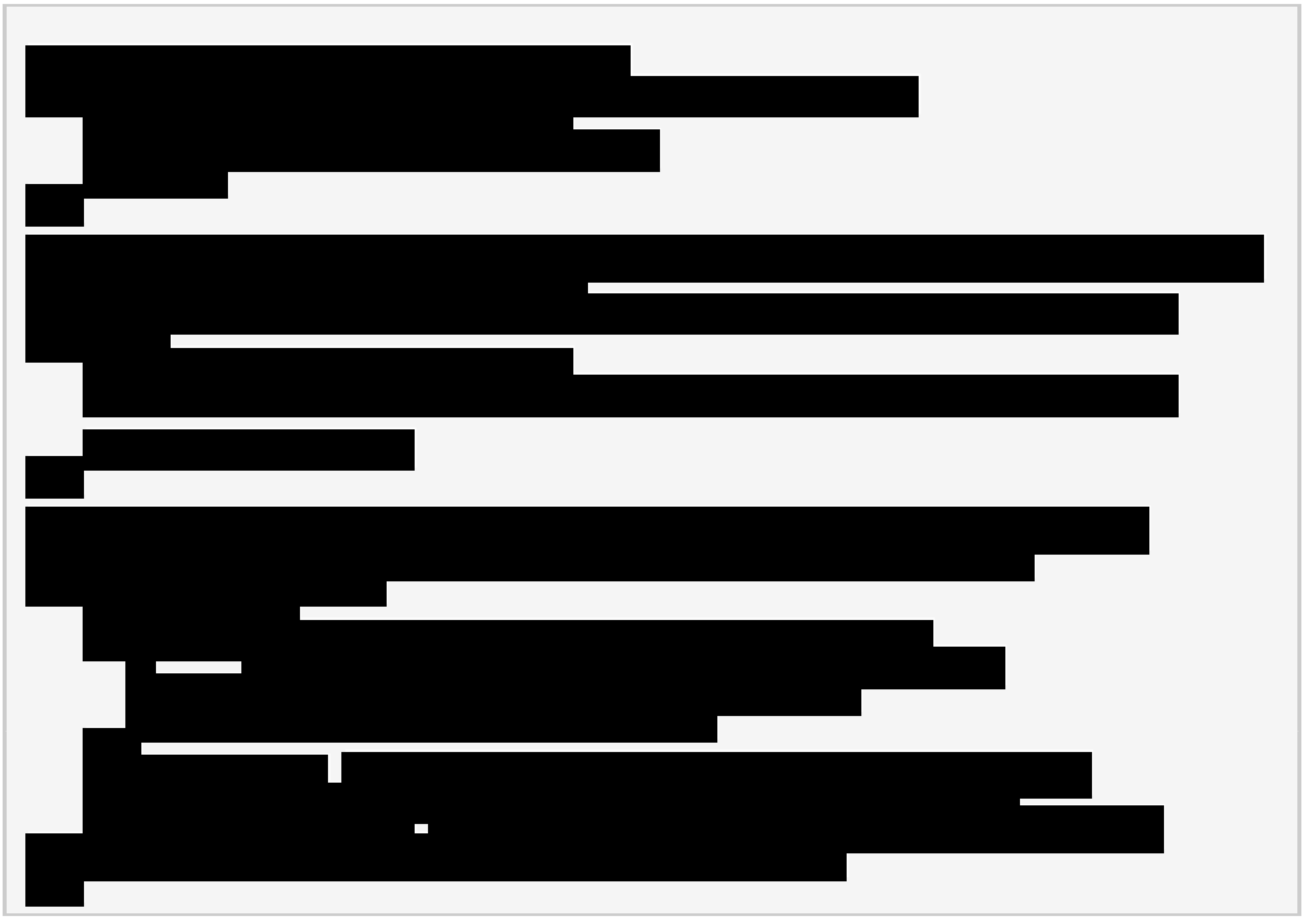
The use of strong CYP2D6 inhibitors or strong CYP3A4 inducers is not permitted during the Double-Blind Treatment Phase of the study, and if being used, should be discontinued at Screening; washout of 5 half-lives or 1 week (whichever is longer) of these medications is required prior to enrollment and initiating study drug. These medications are allowed during the OLE Phase of the study, but adjustment of the dose of pitolisant may be required.

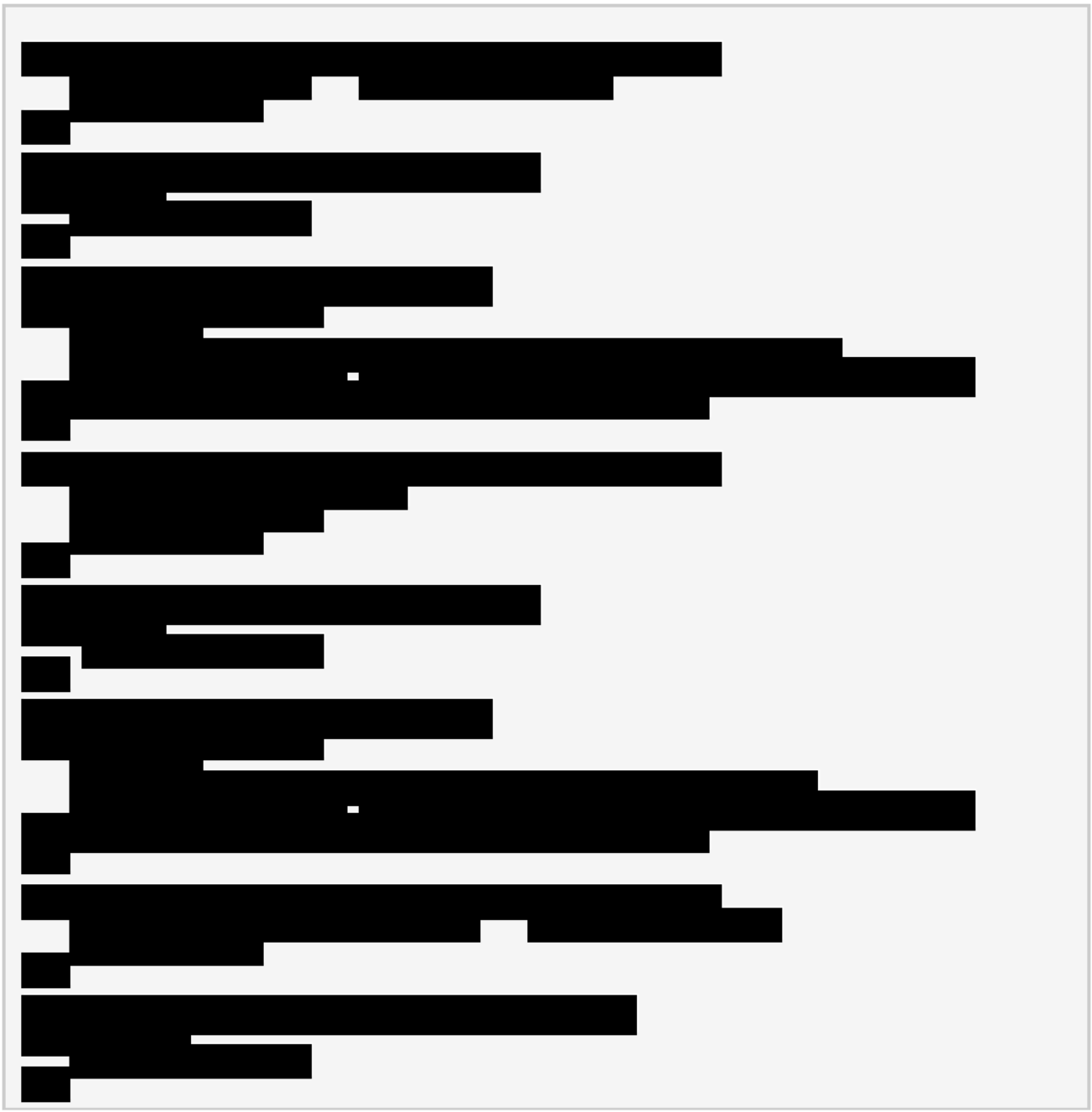
Concomitant use of centrally acting H_1 receptor antagonists is not permitted during the Double-Blind Treatment Phase of the study (requires a washout of 5 half-lives or 1 week, whichever is longer, prior to randomization). Although not prohibited during the OLE Phase of the study, use of these medications should be avoided and, if needed, will require consultation with the Medical Monitor.

Appendix 4 SAS Sample Code

Below are examples of code for the data imputations and inferential statistics described in the SAP.

[redacted]





MMRM:

MIAnalyzed (for the MMRM):

ANCOVA:

Appendix 5 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 6 Clinical Laboratory Tests

Urine Drug Screen -Amphetamines/stimulants[a] -Barbiturates -Benzodiazepines -Cocaine metabolites -Opiates -Tetrahydrocannabinol -Phencyclidine **Urinalysis** -Specific gravity -pH -Blood -Glucose -Protein -Leukocyte esterase -Ketones -Bilirubin -Nitrites -Casts -Crystals -Erythrocytes -Renal tubular epithelial cells -WBCs -Bacteria **Serum Drug Screen** -Cannabidiol **Pregnancy Screen (FCBP only)** -Serum (at Screening only) -Urine (as scheduled after screening)	**Serum Chemistry (5.0 mL blood sample)** -Albumin -Alkaline phosphatase -Alanine aminotransferase -Aspartate aminotransferase -Blood urea nitrogen -Calcium -Chloride -Creatinine -Creatine kinase -Glucose -High-density lipoprotein -Low-density lipoprotein -Phosphorus -Potassium -Sodium -Total bilirubin -Direct bilirubin -Total cholesterol -Total protein -Triglycerides -Uric acid -Ghrelin[b] **Hematology (4.0 mL blood sample)** -Complete blood count, including platelet count and WBC count with differential -Hemoglobin -Hematocrit -HbA1c

Abbreviations: FCBP = female of child-bearing potential; HbA1c = hemoglobin A1c; WBC = white blood cell

[a] Stimulants are tested in the Double-Blind Treatment Phase only.

[b] Acylated and unacylated ghrelin; patient must be fasting. Blood sample for ghrelin measurement may be taken at the same time as clinical laboratory test sample.

Note: Parameters will be assessed at study visits as detailed in the Schedule of Assessments for the Double-Blind Treatment Phase and the Schedule of Assessments for the OLE Phase.

Appendix 7 Schedule of Assessments Double-Blind Treatment Phase

	Screening/Baseline[a] (Maximum 45 days)		Double-Blind Treatment Phase (11 Weeks)										
			Titration Period (3 weeks)[b] Day 1 to 21			Stable Dose Period (8 weeks)[c] Day 22 to 77							
Visit/TC Study Day	Screening VISIT 1 Day -45 to -2	Baseline VISIT 2 Day -1	Day 1[b] (+2 days)	TC 1 Day 8 (±3 days)	TC 2 Day 15 (±3 days)	VISIT 3[d] Day 22 (±3 day)	TC 3 Day 29 (±3 days)	TC 4 Day 36 (±3 days)	VISIT 4[d] Day 50 (±3 days)	TC 5 Day 57 (±3 days)	EOT[e]/ETf VISIT 5 Day 77 (±3 days)	Safety F-Up TCs[g]	Unsch visits[h]
Informed consent	X												
Assess/confirm eligibility	X	X											
Demographics	X												
Medical history	X	X											
Pregnancy test (FCBP)[i]	X	X				X			X		X		
Urine drug screen[j]	X	X									X		
Physical examination[k]	X	X				X			X		X		
Body weight[l]	X	X				X			X		X		X
Height[l]	X										X		X
Vital signs[m]	X	X				X			X		X		X
12-lead ECG (in triplicate)[n]	X	X				X			X		X		
C-SSRS[o]	X	X		X	X	X	X	X	X	X	X	X	
ADAMS	X	X				X	X	X	X	X	X	X	
Clinical laboratory tests[p]	X	X[q]				X			X		X[q]		

	Screening/Baseline[a] (Maximum 45 days)		Double-Blind Treatment Phase (11 Weeks)										
			Titration Period (3 weeks)[b] Day 1 to 21			Stable Dose Period (8 weeks)[c] Day 22 to 77							
Visit/TC Study Day	Screening VISIT 1 Day -45 to -2	Baseline VISIT 2 Day -1	Day 1[b] (+2 days)	TC 1 Day 8 (±3 days)	TC 2 Day 15 (±3 days)	VISIT 3[d] Day 22 (±3 day)	TC 3 Day 29 (±3 days)	TC 4 Day 36 (±3 days)	VISIT 4[d] Day 50 (±3 days)	TC 5 Day 57 (±3 days)	EOT[e]/ETf VISIT 5 Day 77 (±3 days)	Safety F-Up TCs[g]	Unsch visits[h]
Ghrelin measurements		X[q]									X[q]		
Genetic testing[r]	X												
Dispense study diary[s]	X												
Adverse events[t]	X	X		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Randomization		X											
Dispense study drug[u]		X				X			X		X		
Administer/titrate study drug			X[b]	X[b]	X[b]	←		X[c]			→		
Study drug compliance/ accountability				X	X	X	X	X	X	X	X		X
Blood sample for PK						X[v]			X[w]		X[v]		
ESS-CHAD (parent/caregiver version)	X	X				X			X		X		
CaGI-S (of EDS)		X				X			X		X		

	Screening/Baseline[a] (Maximum 45 days)		Double-Blind Treatment Phase (11 Weeks)										
			Titration Period (3 weeks)[b] Day 1 to 21			Stable Dose Period (8 weeks)[c] Day 22 to 77							
Visit/TC Study Day	Screening VISIT 1 Day -45 to -2	Baseline VISIT 2 Day -1	Day 1[b] (+2 days)	TC 1 Day 8 (±3 days)	TC 2 Day 15 (±3 days)	VISIT 3[d] Day 22 (±3 day)	TC 3 Day 29 (±3 days)	TC 4 Day 36 (±3 days)	VISIT 4[d] Day 50 (±3 days)	TC 5 Day 57 (±3 days)	EOT[e]/ETf VISIT 5 Day 77 (±3 days)	Safety F-Up TCs[g]	Unsch visits[h]
CGI-S (overall clinical status related to PWS)		X				X			X		X		
ABC-2		X				X			X		X		
MERS-PWS		X				X			X		X		
Cogstate Detection	X[x]	X							X		X		
Cogstate Identification	X[x]	X							X		X		
Cogstate One Back	X[x]	X							X		X		
ZBI-22		X[bb]				X			X		X		
HQ-CT		X				X			X		X		
FSZQ		X				X			X		X		

Abbreviations: ABC-2 = Aberrant Behavior Checklist, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CaGI-S = Caregiver Global Impression of Severity; CDC = Centers for Disease Control and Prevention; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDS = excessive daytime sleepiness; EOT = end of treatment; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; ET = early termination; FCBP = female of child-bearing potential; FSZQ = Food Safe Zone Questionnaire; F-Up = follow-up; HbA1c = hemoglobin A1c; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-PWS = Montefiore-Einstein Rigidity Scale - Prader-Willi Syndrome; OLE = Open-Label Extension; PK = pharmacokinetic(s); PWS = Prader-Willi syndrome; TC = telephone call; Unsch = unscheduled; ZBI-22 = 22-item Zarit Burden Interview.

[a] In the event that a portion of the Screening Visit is conducted remotely, specific procedures for both the Screening Visit and Baseline Visit will be conducted as detailed in Protocol Section 6.6.

[b] The 3-week Titration Period for the Double-Blind Treatment Phase will be from Days 1 to 21 (±3 days). Patients should take their first dose of study drug on the day after the Baseline Visit (Day 1), and study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized stable dose, Protocol Table 6); all patients will

be at their randomized stable dose of study drug by Day 15. Patients and/or their caregivers will receive TCs on Days 8 and 15 (±3 days) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug.

[c] The 8-week Stable Dose Period in the Double-Blind Treatment Phase will be from Days 22 to 77 (±3 days); patients will take their last dose of blinded treatment on Day 77 ±3 days; study drug compliance will be monitored at TCs and study visits as detailed in Protocol Section 5.5.

[d] In the event that Visit 3 and/or Visit 4 are conducted remotely, specific procedures will be conducted as detailed in Protocol Section 6.6.1.2.

[e] Visit 5 (Day 77 ±3 days) is the EOT visit for the Double-Blind Treatment Phase. Eligible patients who enter the optional OLE Phase will be dispensed open-label pitolisant at this visit (Protocol Section 5.2.2); eligibility criteria must be confirmed before a patient can participate in the OLE Phase.

[f] Patients who prematurely discontinue study drug are required to complete the ET Visit. Procedures to be performed are the same as for the EOT Visit (Protocol Section 7.3.3). Reasons for discontinuation must be recorded.

[g] Patients who do not enter the optional OLE Phase will receive Safety Follow-up TCs from the study site 15 (±3 days) and 30 days (+3 days) after their final dose of blinded treatment to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use.

[h] Unscheduled visits and assessments may be conducted by telephone or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator (Protocol Section 7.6).

[i] Serum pregnancy test is to be performed at Screening and a urine pregnancy test is to be performed at all other visits, as indicated.

[j] Urine drug screen as detailed in Protocol Table 9 is to be performed at the Screening Visit, Baseline Visit (on Visit 2), and at Visit 5 (Day 77).

[k] Full physical examination is to be performed at the Screening Visit and Visit 5 (Day 77); abbreviated physical examination is to be performed at Visits 2, 3 and 4 (Protocol Section 6.5.2).

[l] Height and weight will be measured using standardized methods and recorded on a standardized growth chart (CDC Clinical Growth Charts).

[m] Vital signs include blood pressure, heart rate, respiratory rate, and body temperature; patients should be resting for at least 5 minutes before measuring vital signs.

[n] Perform 12-lead ECGs (in triplicate) after the patient has been resting for at least 5 minutes. Any clinically significant ECG reading should be promptly addressed by the Investigator as detailed in Protocol Section 6.5.4.

[o] At Screening, suicidality is to be assessed through use of the Very Young Child/Cognitively Impaired–Lifetime Recent C-SSRS. (Protocol Appendix L). At all other study visits and TCs, suicidality will be assessed through use of the Very Young Child/Cognitively Impaired–Since Last Contact C-SSRS (Protocol Appendix M).

[p] Clinical laboratory tests (serum chemistry, hematology, urinalysis) to include lipid profile and HbA1c (Protocol Table 9); laboratory tests may be repeated at unscheduled visits if necessary.

[q] Ghrelin measurement is to be done fasting; clinical laboratory tests, including PK sample at Visit 5, may be done with the fasting ghrelin test.

[r] Genetic testing will be provided by the Sponsor for patients who do not have documented genetic confirmation of PWS diagnosis based on the review of the patient's medical records.

[s] Patients will be dispensed a study diary containing a sleep diary section and a study drug dosing section at the Screening Visit (Protocol Appendix B).

[t] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient/parent(s)/legal guardian(s) provides written informed consent/assent through 30 days (+3 days) after final dose of study drug (Safety Follow-up TCs, Protocol Section 7.5). At the Safety Follow-up TCs, AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded , and the C-SSRS and ADAMS will be completed.

[u] Patients will be instructed to take study drug once daily in the morning upon wakening; exception is on the morning of Visit 4, when study drug administration will be at the study site, with the timing of administration based on the PK sampling schedule. Patients will be instructed to record in the study drug dosing section of the study diary (with the assistance of their caregiver if needed) the number of tablets administered from each bottle daily (Protocol Appendix B); the time of study drug dosing will be recorded on the day before Study Visit 4.

[v] Blood sample collection for PK analyses at Visit 3 and Visit 5 may be at any time after the morning dose of study drug and samples may be collected at the same time as the clinical laboratory sample (including the fasting ghrelin sample at Visit 5). Time of last dose of study drug and time of blood sample collection for PK analyses must be recorded.

[w] Patients and/or their caregiver will be instructed to record in the study drug dosing section of the study diary the time of day that they take study drug on the day before Visit 4. On the day of Visit 4, **patients will not take their daily dose of study drug before arriving at the study site.** Study drug administration will be at the study site and timing will be based on the PK sampling schedule. At the study site, a blood sample for PK analyses will be collected before administration of the daily dose of study drug. The time

of study drug administration will be recorded. Blood sample collection for PK analyses will be at the following times after study drug administration: between 45 and 75 minutes after dosing, between 1.5 and 2.5 hours after dosing, between 3.0 and 4.0 hours after dosing, and between 5.0 and 6.0 hours after dosing. The time of each blood sample collection for PK analyses is to be recorded. The total volume of blood collected is not to exceed the maximal allowable of 3.0 mL/kg per day (Protocol Appendix A and Table 8).

[x] To familiarize patients with the Cogstate Computerized Cognitive Test Battery, the tests are to be administered twice during Screening with a break of at least 15 minutes between battery administrations.

Assessments associated with on-site study visits during the Double-Blind Treatment Phase may be completed remotely, under the oversight of the Investigator, as detailed in Protocol Section 6.7.

Appendix 8 Schedule of Assessments Open-Label Extension Phase

	OLE 3-Week Titration Period[a] Day 78 to Day 98			OLE Long-Term Dosing Period[b] Day 99 to End of Treatment[c]						
	Month 3			On-site Visits Months 4, 6, 9, and 12[d]		Telephone Calls Month 15 then every 6 months	On-site Visits Month 18 then every 6 months[d]			
Visit/TC Study Day	Day 78 (±3 days)	TC 6 Day 85 (±3 days)	TC 7 Day 92 (±3 days)	VISIT 6 Day 99 (±3 days) and VISIT 8 Day 279 (±7 days)	VISIT 7 Day 189 (±7 days) and VISIT 9 Day 369 (±7 days)	TC 8[e] Day 459 (±7 days) then every 180 Days (±7 days) through EOS	VISIT 10[e] Day 549 (±7 days) then every 180 Days (±7 days) through EOS	EOT[f]/ET[g] Visit	Safety F-Up TCs[h]	Unsch visits[i]
Urine pregnancy test (FCBP)				X	X		X	X		
Full physical examination				X	X		X	X		
Body weight and height[j]				X	X		X	X		X
Clinical laboratory tests[k]				X	X		X	X		
Urine drug screen[l]				X	X		X	X		
Vital signs[m]				X	X		X	X		X
12-lead ECG (in triplicate)[n]				X	X		X	X		
C-SSRS[o]		X	X	X	X	X	X	X		
ADAMS				X	X		X	X	X	
Dispense/confirm receipt of pitolisant[p]				X	X	X	X			
Study drug compliance and accountability		X	X	X	X	X	X	X		X

Visit/TC Study Day	OLE 3-Week Titration Period[a] Day 78 to Day 98			OLE Long-Term Dosing Period[b] Day 99 to End of Treatment[c]					Safety F-Up TCs[h]	Unsch visits[i]
	Month 3			On-site Visits Months 4, 6, 9, and 12[d]		Telephone Calls Month 15 then every 6 months	On-site Visits Month 18 then every 6 months[d]			
	Day 78 (±3 days)	TC 6 Day 85 (±3 days)	TC 7 Day 92 (±3 days)	VISIT 6 Day 99 (±3 days) and VISIT 8 Day 279 (±7 days)	VISIT 7 Day 189 (±7 days) and VISIT 9 Day 369 (±7 days)	TC 8[e] Day 459 (±7 days) then every 180 Days (±7 days) through EOS	VISIT 10[e] Day 549 (±7 days) then every 180 Days (±7 days) through EOS	EOT[f]/ET[g] Visit		
Administer/titrate pitolisant	X[a]	X[a]	X[a]	←		X[b]		→		
Adverse events[q]		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
ESS-CHAD (parent/caregiver version)				X	X		X	X		
CaGI-S (of EDS)				X	X		X	X		
CGI-S (overall clinical status related to PWS)				X	X		X	X		
ABC-2				X	X					
MERS-PWS					X					
Cogstate Detection					X					
Cogstate Identification					X					
Cogstate One Back					X					
ZBI-22				X	X					
HQ-CT				X	X					
FSZQ				X	X					

Abbreviations: ABC-2 = Aberrant Behavior Checklist, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CaGI-S = Caregiver Global Impression of Severity; CDC = Centers for Disease Control and Prevention; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating; ECG = electrocardiogram; EDS = excessive daytime sleepiness; EOS = end of study; EOT = end of treatment; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; ET = early Termination; FCBP = female of child-bearing potential; FSZQ = Food Safe Zone Questionnaire; F-Up = follow-up; HbA1c = hemoglobin A1c; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-PWS = Montefiore-Einstein Rigidity Scale-Prader-Willi Syndrome; OLE = Open-Label Extension; PWS = Prader-Willi syndrome; TC = telephone call; Unsch = unscheduled; ZBI-22 = 22-item Zarit Burden Interview.

[a] Eligible patients who enter the OLE Phase will begin a 3-week titration period after completion of the Double-Blind Treatment Phase of the study. The Titration Period for the OLE Phase will start on Day 78 (±3 days), i.e., the day after the EOT visit (Visit 5) in the Double-Blind Treatment Phase and will end on Day 98 (±3 days). Pitolisant doses will be titrated to a target dose (based on age); first day of open-label treatment is on Day 78 (±3 days), and pitolisant dose will be titrated on Day 85 (±3 days) and again on Day 92 (±3 days), as outlined in Protocol Table 7. Patients and/or their caregivers will receive TCs on Days 85 and 92 (±3 days) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of pitolisant dose. Pitolisant doses may be adjusted as detailed in Protocol Section 3.1.5.2.

[b] At the end of the 3-week OLE Titration Period, patients will continue to take open-label pitolisant once daily in the morning upon wakening through the end of the study (Long-Term Dosing Period). Adjustments to pitolisant dose are permitted as detailed in Protocol Section 3.1.5.2.

[c] The Long-Term Dosing Period for the OLE Phase will be from Day 99 (±3 days) until either pitolisant is approved for patients with PWS or the Sponsor elects to terminate the study.

[d] Patients will have the option to complete up to two of the scheduled on-site study visits (i.e., Visits 6, 7, 8, and 9) remotely; thereafter (i.e., after Visit 9/Month 12), patients may complete one of the scheduled on-site visits remotely per year. Assessments associated with on-site study visits that may be completed remotely, under the oversight of the Investigator, are detailed in Protocol Section 6.6.

[e] Patients and/or their caregivers will receive a TC on Day 459 (±7 days; TC 8) and will return with their caregivers to the study site for an on-site visit on Day 549 (±7 days; Visit 10). Patients will continue to have alternating TCs and on-site study visits approximately every 3 months (90 days ±7 days) thereafter until the end of the study. The TCs will be to record AEs and concomitant medication use, complete the C-SSRS, confirm the current dose of study drug and compliance with dosing, and confirm shipment/receipt of study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration. Safety and efficacy evaluations performed at the on-site study visits will be the same as those outlined for Visit 10. Study drug compliance will be monitored at TCs and study visits as detailed in Protocol Section 5.5.

[f] All patients will complete an EOT Visit (Protocol Section 7.4.2.4). The safety and efficacy evaluations to be performed are the same as those listed for Visit 10.

[g] Patients who prematurely discontinue study drug are required to complete the ET Visit (Protocol Section 7.4.3). Reasons for discontinuation must be recorded.

[h] All patients and/or their caregiver will receive Safety Follow-up TCs from the study site 15 (±3 days) and 30 days (+3 days) after their final dose of open-label pitolisant to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use.

[i] Unscheduled visits and assessments may be conducted by telephone or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator (Protocol Section 7.6).

[j] Height and weight will be measured using standardized methods and recorded on a standardized growth chart (CDC Clinical Growth Charts).

[k] Clinical laboratory tests (serum chemistry, hematology, urinalysis) to include lipid profile and HbA1c (Protocol Table 9); laboratory tests may be repeated at unscheduled visits if necessary.

[l] Protocol Table 6 provides a list of drugs that are tested.

[m] Vital signs include blood pressure, heart rate, respiratory rate, and body temperature; patients should be resting for at least 5 minutes before measuring vital signs.

[n] Perform 12-lead ECGs (in triplicate) after the patient has been resting for at least 5 minutes. Any clinically significant ECG reading should be promptly addressed by the Investigator as detailed in Protocol Section 6.5.4.

[o] Suicide risk/suicidality will be assessed at all study visits and TCs using the Very Young Child/Cognitively Impaired-Since Last Contact C-SSRS (Protocol Appendix M).

[p] During the OLE Phase, open-label pitolisant in a quantity sufficient for 90 days of once daily administration will be provided to patients every 3 months (90 days) either via mail or at the on-site study visits. Patients will be instructed to take pitolisant once daily in the morning upon wakening.

[q] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient/parent(s)/legal guardian(s) provides written informed consent/assent through 30 days (+3 days) after final dose of open-label pitolisant (Safety Follow-up TCs, Protocol Section 7.5). At the Safety Follow-up TCs, AEs (including inquiries regarding signs

and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded, and the ADAMS will be completed.

Assessments associated with on-site study visits during the OLE Phase may be completed remotely, as directed and overseen by the Investigator, and detailed in Protocol Section 6.6.