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

NCT Number: NCT04257929

Protocol Date (last revision date): August 10, 2023

CLINICAL STUDY PROTOCOL: HBS-101-CL-002

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
IND Number	143663
Investigational Product:	Pitolisant (also referred to as HBS-101)
Phase of Development:	2
Sponsor:	Harmony Biosciences, LLC 630 W. Germantown Pike, Suite 215 Plymouth Meeting, PA 19462 USA
Protocol Version:	Amendment 6
Effective Date:	10AUG2023

SPONSOR SIGNATURE

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
Protocol Number:	HBS-101-CL-002, Amendment 6

This protocol Amendment 6 has been reviewed and approved by the Sponsor.

Signature: Date: 10AUG2023

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HBS-101-CL-002

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

I have received and read the current Investigator's Brochure for pitolisant. I have read the HBS-101-CL-002 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Confidentiality Statement

The confidential information in this document is provided to you as the Principal Investigator for review by you, your staff, and the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Harmony Biosciences, LLC
NAME OF FINISHED PRODUCT(S):	Pitolisant tablets (also referred to as HBS-101)
NAME OF ACTIVE INGREDIENT(S):	Pitolisant hydrochloride (also referred to as HBS-101)
PROTOCOL NUMBER:	HBS-101-CL-002
PHASE OF DEVELOPMENT:	2

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

NUMBER OF PLANNED PATIENTS: Approximately 60 patients (ages 6 to 65 years) with Prader-Willi syndrome (PWS)

STUDY SITES: Approximately 15 sites in the United States (US)

STUDY OBJECTIVES:

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 PWS ages 6 to 65 years.

Secondary Objectives

Key Secondary Objectives

The key secondary objectives of this study are 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.

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

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 ghrelin levels
- The pharmacokinetics (PK) of pitolisant and its major metabolite, BP1.3484
- The relationship between levels of pitolisant (PK) and treatment effect (pharmacodynamics)

METHODOLOGY:

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 Open-Label Extension (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 will be multi-year in duration and will continue until the Sponsor elects to terminate the study.

After completing the Screening Period, eligible patients will be enrolled into the Double-Blind Treatment Phase of the study.

The Double-Blind Treatment Phase of the study will be 11 weeks, which includes a 3-week Titration Period and an 8-week Stable Dose Period. Eligible patients will be randomized in a 1:1:1 ratio to receive treatment with lower dose pitolisant, higher dose pitolisant, or matching placebo (20 patients per treatment group, ages 6 to 65 years). The lower and higher 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. In the Double-Blind Treatment Phase, patients will be titrated to their randomized stable dose of study drug during the 3-week Titration Period. After completion of the 3-week Titration Period, patients will continue to take study drug at their randomized stable dose once daily in the morning upon wakening for an additional 8 weeks of blinded treatment (Stable Dose Period). The duration of the Double-Blind Treatment Phase will be 11 weeks. Patients and/or their caregiver will receive telephone calls (TCs) from the study site on Days 8 and 15 (±3 days) (TCs 1 and 2, respectively) during the 3-week Titration Period to assess for adverse events (AEs) and concomitant medication use, complete the Columbia-Suicide Severity Rating Scale (C-SSRS), and review/confirm titration of study drug. During the 8-week Stable Dose Period, patients will complete safety, efficacy, and PK assessments at the study site on Day 22 (Visit 3), Day 50 (Visit 4), and Day 77 (Visit 5) (window for Visits 3, 4, and 5 is ±3 days), and patients and/or their caregiver will receive TCs from the study site on Days 29, 36, and 57 (±3 days; TCs 3, 4, and 5, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS and Anxiety, Depression, and Mood Scale (ADAMS), and confirm study drug dose. Specific procedures and assessments for Screening (Visit 1), Visit 3, and Visit 4 may be conducted remotely as detailed in Section 6.6.

At the end of the Double-Blind Treatment Phase, eligible patients will be given the opportunity to enter an optional OLE Phase. If a patient does not enter the OLE Phase, the patient and/or their caregiver will receive Safety Follow-up TCs from the study site 15 days (±3 days) and 30 days (+3 days) after their final dose of blinded treatment.

In the OLE Phase, prior to implementation of Amendment 6 of the protocol, patients received a maximum target dose of pitolisant 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). [redacted] Adjustments to pitolisant dose are allowed during the OLE Phase based on Investigator discretion in consultation with the Medical Monitor up to the maximum daily dose allowed [redacted].

In the OLE Phase, patients and/or their caregivers will receive TCs from the study site on Days 85 and 92 (±3 days; TCs 6 and 7, respectively) and will return to the study site for assessment of safety and effectiveness on Days 99 (Visit 6), 189 (Visit 7), 279 (Visit 8), and 369 (Visit 9) (window for Visits 6, 7, 8, and 9 is ±7 days). After completion of Visit 9, patients and/or their caregivers will receive a TC from the study site on Day 459 (TC 8), and patients will complete an on-site study visit on Day 549 (Visit 10); this pattern of alternating TCs and on-site study visits approximately every 3 months will be repeated until either the patient withdraws from the study or the study is terminated by the Sponsor (window for all TCs and study visits after Visit 9 is ±7 days). 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. Remote visits cannot be consecutive. Specific procedures and assessments that may be conducted remotely are detailed in Section 6.6.

STUDY POPULATION:

Approximately 60 patients with PWS are planned to be enrolled in the study at approximately 15 sites in the US.

Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is able to provide voluntary, written informed consent (patient or parent[s]/legal guardian[s]) and, where applicable, voluntary, written assent (patient, as appropriate).
2. Has a diagnosis of PWS confirmed by genetic testing and/or patient medical records. Genetic testing will be provided by the Sponsor, if not confirmed based on the review of the patient's medical records.
3. Male or female patients ages 6 to 65 years at the time of enrollment.
4. Demonstrates adequate sleep duration via patient sleep diary during Screening, defined as at least 8 hours of sleep per night for patients ages 6 to <12 years, at least 7 hours for patients ages 12 to <18 years, or at least 6 hours for patients ages ≥18 years, based on the mean number of hours from up to 14 nights (at least 7 nights must be recorded for evaluation).
5. Has EDS as determined by Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) (parent/caregiver version) score of ≥12.
6. If taking hormone treatments (including growth hormone, testosterone, and estrogen supplements) and/or allowed chronic concomitant medication or supplements, patient must be on a stable dose of these medications for 3 months prior to randomization and for the duration of the Double-Blind Treatment Phase of the study; a 10% variability in hormone dose is allowed.
7. If taking a wake-promoting treatment that could affect EDS (including stimulants, modafinil, and armodafinil), must be on a stable dose for at least 28 days prior to Screening and remain on a stable dose during the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.
8. If taking a chronically administered sedating medication for management of behavioral manifestations (e.g., hypnotics, benzodiazepines, antipsychotics, alpha agonists, anticholinergics, and antidepressants) must be on a stable dose for at least 28 days prior to Screening and remain on a stable dose during the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.
9. If using cannabidiol and/or tetrahydrocannabinol, patient must be on a stable dose for 28 days prior to randomization and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase).
10. If taking oxytocin or carbetocin, patient must be on a stable dose during the 28 days prior to randomization and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.

11. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Baseline Visit and agree to remain abstinent or use an effective method of nonhormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
12. Has a consistent caregiver (preferably the same person throughout the Double-Blind Treatment Phase of the study) who is willing and able to complete the required assessments.
13. In the opinion of the Investigator, patient/parent(s)/legal guardian(s) is capable of understanding and complying with the requirements of the protocol and administration of oral study drug.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from enrollment in the study:

1. Has a diagnosis of another genetic or chromosomal disorder distinct from PWS.
2. Has untreated obstructive sleep apnea (OSA) or is at high risk for OSA based on medical history and clinical assessment; or, has another relevant underlying sleep disorder that in the opinion of the Investigator is the primary contributing factor to the patient's EDS.
3. Consistently consumes >600 mg of caffeine per day and is unable/unwilling to reduce caffeine intake to <600 mg per day for the duration of the Double-Blind Treatment Phase of the study; caffeine intake should remain consistent during Screening and throughout the Double-Blind Treatment Phase of the study.
4. Does not agree to discontinue any prohibited medication or substance listed in the protocol (Section 5.7.2).
5. Participation in an interventional research study involving another investigational medication or device in the 28 days prior to enrollment and for the duration of the Double-Blind Treatment Phase of the study, unless the Investigator consults with the Medical Monitor and obtains written approval for the patient to enroll; patients who complete a washout of an investigational medication of at least 5 half-lives or 14 days (whichever is longer) may be enrolled in the Double-Blind Treatment Phase of the study. Patients considering participation in another interventional research study in the OLE Phase must consult with the Investigator who will consult with the Medical Monitor.
6. Has a primary psychiatric diagnosis with current active symptoms of psychosis or schizophrenia.
7. Has a diagnosis of end-stage renal disease (estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).
8. Has a diagnosis of moderate or severe renal impairment (eGFR ≥15 to ≤59 mL/minute/1.73 m^2) or moderate hepatic impairment (Child-Pugh B) at Screening or during the Double-Blind Treatment Phase.
9. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.
10. Has a known history of long QT syndrome or any significant history of a serious abnormality of the electrocardiogram (ECG; e.g., recent myocardial infarction, clinically significant arrhythmia) or QT interval corrected for heart rate according to Fridericia's formula (QTcF) >442 ms for patients ages 0 to <10 years and >439 ms for patients ages 10 to <20 years, regardless of gender, and >450 ms for

male patients and >470 ms for female patients ages 20 to 65 years. (ECG QTcF = QT/3√ RR) (Mason et al 2007).

11. Has a family history of sudden/unexplained death, cardiac death, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member.
12. If receiving any new or initiating a change in allied health therapies or interventions for symptoms of PWS, must be on a stable course of therapy for at least 28 days prior to randomization.
13. Has a current or recent (within one year) history of a substance use disorder or dependence disorder, including alcohol and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).
14. Has planned surgery during the Double-Blind Treatment Phase of the study; planned surgery is permitted during the OLE Phase.
15. Is receiving a concomitant medication that is known to be a strong cytochrome P450 (CYP) 2D6 inhibitor, a strong CYP3A4 inducer, or a centrally acting histamine 1 (H_1) receptor antagonist; patients who complete a washout of these medications of at least 5 half-lives or 14 days (whichever is longer) can be enrolled in the Double-Blind Treatment Phase of the study. Use of strong CYP2D6 inhibitors and strong CYP3A4 inducers is allowed during the OLE Phase; however, adjustment of pitolisant dose is required (Section 5.7.3). Although not prohibited during the OLE Phase of the study, use of H_1 receptor antagonists should be avoided.
16. Is receiving a medication known to prolong the QT interval.
17. Has a significant risk of committing suicide based on history, routine psychiatric examination, Investigator's judgment, or an answer of "yes" on any question other than questions 1 to 3 on the Very Young Child/Cognitively Impaired-Lifetime Recent Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix L).
18. Has a history of seizures that have recently (within 6 months) been treated with antiepileptic medications that are strong CYP3A4 inducers. Patients with a history of seizures must have a stable seizure history (e.g., frequency and severity) for at least 6 months prior to enrollment.
19. Is currently breastfeeding or planning to breastfeed over the course of the study. Lactating women must agree not to breastfeed for the duration of the study (Double-Blind Treatment Phase and OLE Phase) and for 21 days after final dose of study drug.
20. Based on the judgment of the Investigator, patient is unsuitable for the study for any reason, including but not limited to unstable or uncontrolled medical conditions (including psychiatric and neurological conditions) or a medical condition that might interfere with the conduct of the study, confound interpretation of study results, pose a health risk to the patient, or compromise the integrity of the study.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION: Pitolisant tablets containing 4.45 mg and 17.8 mg pitolisant base will be administered orally once daily in the morning upon wakening.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION: During the Double-Blind Treatment Phase of the study, matching placebo tablets will be administered orally once daily in the morning upon wakening.

DURATION OF TREATMENT: The study is expected to be multi-year in duration. The Double-Blind Treatment Phase will remain open until the last patient completes this phase of the study and the OLE Phase will remain open until the Sponsor elects to terminate the study.

The duration of participation for individual patients in the Double-Blind Treatment Phase is expected to be up to approximately 21 weeks, including a maximum of 45 days of screening, 11 weeks of double-blind treatment (includes a 3-week Titration Period and an 8-week Stable Dose Period), and 30 days of safety follow-up for patients who do not enter the OLE Phase. For patients who enter the OLE Phase of the study, individual patient participation is expected to be multi-year in duration.

STUDY ASSESSMENTS: Efficacy, safety, and PK will be assessed.

Efficacy assessments will include ESS-CHAD (parent/caregiver version), Caregiver Global Impression of Severity (CaGI-S) for EDS, Clinical Global Impression of Severity (CGI-S) for overall clinical status related to PWS, Aberrant Behavior Checklist-Community, Second Edition (ABC-C), Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS (MERS-R-PWS), Cogstate Detection Test, Cogstate Identification Test, Cogstate One Back Test, 22-item Zarit Burden Interview (ZBI-22), Hyperphagia Questionnaire for Clinical Trials (HQ-CT) in conjunction with the Food Safe Zone Questionnaire (FSZQ), and acylated and unacylated fasting ghrelin levels.

Safety assessments will include evaluation of AEs, vital signs, 12-lead ECGs, physical examinations, clinical laboratory test results, and other safety assessments (suicidality, anxiety, and monitoring of seizures in patients with seizure disorder).

Pharmacokinetic assessments will include maximum observed concentration (C_{max}), area under the concentration-time curve (AUC) from time 0 to the last collection time (AUC_{last}), and time to observed maximum concentration (t_{max}) of pitolisant and its major metabolite, BP1.3484.

Some assessments associated with on-site study visits may be completed remotely, as directed and overseen by the Investigator and detailed in Section 6.6.

STUDY ENDPOINTS:

EFFICACY ENDPOINTS

Double-Blind Treatment Phase:

Primary Efficacy Endpoint

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

Key Secondary Efficacy Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- CaGI-S for EDS
- CGI-S for overall clinical status related to PWS

Other Secondary Efficacy Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- Behavior as measured by the ABC-C
- Behavioral and cognitive rigidity as measured by the MERS-R-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

Exploratory Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- Total score of the HQ-CT in conjunction with the FSZQ
- Acylated and unacylated ghrelin levels

Open-Label Extension Phase

Long-term effectiveness of pitolisant as measured by ESS-CHAD (parent/caregiver version), CaGI-S for EDS, CGI-S for overall clinical status related to PWS, ABC-C, MERS-R-PWS, Cogstate Detection Test, Cogstate Identification Test, Cogstate One Back Test, ZBI-22, and HQ-CT in conjunction with the FSZQ will be assessed during the first year of participation (through Visit 9) in the OLE Phase of the study. After the first year, only ESS-CHAD (parent/caregiver version), CaGI-S, and CGI-S will continue to be assessed.

PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINTS

- C_{max} of pitolisant and its major metabolite, BP1.3484
- AUC_{last} after administration of pitolisant
- t_{max} of pitolisant
- Exposure-response relationship between pitolisant levels and change in efficacy measures

SAFETY ENDPOINTS

Safety will be assessed by monitoring the incidence of AEs and changes in clinical laboratory test results, vital signs, and 12-lead ECG results, along with additional safety assessments (suicidality, anxiety, and monitoring of seizures in patients with seizure disorder) from Baseline to Week 11 in the Double-Blind Treatment Phase and from Baseline to study completion in the OLE Phase.

STATISTICAL METHODS: All analyses will be performed using SAS® version 9.4 or higher, unless otherwise specified.

Primary Efficacy Analyses: Summary statistics (mean, standard deviation, median, minimum, maximum) for the primary efficacy endpoint of change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for pitolisant compared with placebo will be reported by treatment group and for the active groups combined. The change from Baseline will be analyzed in a mixed model repeated measures (MMRM) analysis. Fixed effects will be included for treatment, visit, treatment*visit interaction, Baseline value, and site. An unstructured covariance matrix will be utilized and if this fails to converge, then first-order autoregressive and compound symmetry will be attempted in that order; Kenward-Rogers degrees of freedom will be used. Least square (LS) means, standard errors, and the LS mean differences (each treatment vs placebo and the pooled active groups vs 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 contrast of interest is the difference in the higher dose group versus placebo at Week 11.

Secondary Efficacy Analyses: Continuous outcomes collected at multiple time points will be analyzed with summary statistics (mean, standard deviation, median, minimum, maximum) for the absolute values and change from baseline at each timepoint by treatment group and for the active groups combined. The change from Baseline will be analyzed using an MMRM approach. Fixed effects will be included for treatment, visit, treatment×visit interaction, and baseline value. An unstructured covariance matrix will be utilized and if this fails to converge, then first-order autoregressive and compound symmetry will be attempted in that

order; Kenward-Rogers degrees of freedom will be used. Least square means, standard errors, and the LS mean differences (each treatment vs placebo and the pooled active groups vs placebo) at each time point 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 contrast of interest is the difference in the higher dose group versus placebo at Week 11.

OLE Efficacy Analyses: Results 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. Baseline for the OLE will be the pre-double-blind-treatment baseline (identical to that used for the double-blind analyses). Details of open-label analyses will be fully described in the statistical analysis plan (SAP).

Safety Analyses: All safety data will be listed and summarized for the Double-Blind Treatment Phase and OLE separately in a similar tabulation format as for efficacy. No formal statistics will be performed for the safety analysis.

Determination of Sample Size: The sample size is 60 patients (20 in the lower dose pitolisant group, 20 in the higher dose pitolisant group, and 20 in the placebo group). Prior research suggests that the ESS-CHAD (parent/caregiver version) SD falls between 5 to 6; at the lower end of this range, the study would be powered at 80% to detect a difference of 3.9 between the pooled pitolisant groups and placebo group. However, as a proof of concept study, statistical separation is not a strict objective of the trial. The proposed sample size will yield a 95% confidence interval of ±2.7 with an SD of 5 and ±3.2 with an SD of 6; this will give sufficient precision to inform future studies.

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]/ET[f] 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]		
Ghrelin measurements		X[q]									X[q]		
Genetic testing[r]	X												
Dispense study diary[s]	X												

Visit/TC Study Day	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							
	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]/ET[f] VISIT 5 Day 77 (±3 days)	Safety F-Up TCs[g]	Unsch visits[h]
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		
CGI-S (overall clinical status related to PWS)		X				X			X		X		
ABC-C		X				X			X		X		
MERS-R-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				X			X		X		
HQ-CT		X				X			X		X		
FSZQ		X				X			X		X		

ABC-C = Aberrant Behavior Checklist-Community, 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-R-PWS = Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS; 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 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, Table 7); 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 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 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 (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 (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 (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 Table 11 is to be performed at the Screening Visit, Baseline Visit (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 (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 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. (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 (Appendix M).

[p] Clinical laboratory tests (serum chemistry, hematology, urinalysis) to include lipid profile and HbA1c (Table 11); 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 (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, 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 (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 (Appendix A and Table 10).

[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 Section 6.6.

SCHEDULE OF ASSESSMENTS OPEN-LABEL EXTENSION PHASE

	OLE 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 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]			
	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]
Administer/titrate pitolisant	X	X	X	←	→	X	→			
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-C				X	X					
MERS-R-PWS					X					
Cogstate Detection					X					
Cogstate Identification					X					
Cogstate One Back					X					
ZBI-22				X	X					
HQ-CT				X	X					
FSZQ				X	X					

ABC-C = Aberrant Behavior Checklist-Community, 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-R-PWS = Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS; 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 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. 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 pitolisant doses. Pitolisant doses may be adjusted as detailed in Section 3.1.5.2.

[b] At the end of the 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 Section 3.1.5.2.

[c] The Long-Term Dosing Period for the OLE Phase will continue until 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 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 Section 5.5.

[f] All patients will complete an EOT Visit (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 (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 (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 (Table 11); laboratory tests may be repeated at unscheduled visits if necessary.

[l] Table 11 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 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 (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, 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 Section 6.6.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC-C	Aberrant Behavior Checklist-Community, Second Edition
ADAMS	Anxiety, Depression, and Mood Scale
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the concentration-time curve
AUC_{last}	AUC from time 0 to the last collection time
AUC_{tau}	AUC during a dosing interval at steady state
BMI	Body mass index
CaGI-S	Caregiver Global Impression of Severity
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression of Severity
cGCP	Current Good Clinical Practice
COVID-19	Coronavirus disease 2019
C_{max}	Maximum observed concentration
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation
CYP	Cytochrome P450
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	Ethics Committee
ECG	Electrocardiogram, electrocardiography
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
ESS-CHAD	Epworth Sleepiness Scale for Children and Adolescents
ET	Early Termination

Abbreviation	Definition
EU	European Union
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
FSZQ	Food Safe Zone Questionnaire
GCP	Good Clinical Practice
H_1	Histamine 1
H_3	Histamine 3
ICF	Informed consent form
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LOE	Lack of efficacy
LS	Least square
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MERS-R	Montefiore-Einstein Rigidity Scale-Revised
MERS-R-PWS	Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS
MMRM	Mixed effect model repeated measures
MI	Multiple imputation
NIH	National Institutes of Health
OSA	Obstructive sleep apnea
OLE	Open-Label Extension
PK	Pharmacokinetic(s)
POC	Proof of concept

Abbreviation	Definition
PWS	Prader-Willi syndrome
QTcF	QT interval corrected for heart rate based on Fridericia's formula
REM	Rapid eye movement
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
sTST	Subjective total sleep time
TC	Telephone call
TEAE	Treatment-emergent adverse event
t_{max}	Time to observed maximum concentration
TOB	Time Out of Bed
US	United States (of America)
USPI	United States Prescribing Information
ZBI-22	22-item Zarit Burden Interview

Note: abbreviations used only in tables, figures, or an appendix are defined in the table or figure footnotes or in the appendix.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	Effective Date
Amendment 6	10AUG2023
Amendment 5, Administrative letter	04APR2023
Amendment 5	13DEC2021
Amendment 4	02AUG2021
Amendment 3	05MAY2021
Amendment 2, Administrative letter	15AUG2020
Amendment 2	19JUN2020
Amendment 1	08MAY2020
Original Protocol	05MAR2020

SUMMARY OF CHANGES, AMENDMENT 6

Table 1 describes the changes made in Amendment 6 of the protocol. Minor editorial changes and changes related to abbreviations, punctuation, template language, and formatting (i.e., changes in numbering, word order, location), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

[redacted]

[redacted]

SUMMARY OF CHANGES, AMENDMENT 5, ADMINISTRATIVE LETTER

[redacted]

This change was sent to Investigators in an administrative letter dated 04APR2023.

SUMMARY OF CHANGES, AMENDMENT 5

Table 2 describes the changes made in Amendment 5 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

[redacted]

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[redacted]

SUMMARY OF CHANGES, AMENDMENT 4

Table 3 describes the changes made in Amendment 4 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

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SUMMARY OF CHANGES, AMENDMENT 3

Table 4 describes the changes made in Amendment 3 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

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Section Number and Title	Description of Change	Rationale
[redacted]	[redacted]	[redacted]
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SUMMARY OF CHANGES, AMENDMENT 2, ADMINISTRATIVE LETTER

[redacted]

[redacted]

SUMMARY OF CHANGES, AMENDMENT 2

Table 5 describes the changes made in Amendment 2 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

[redacted]

SUMMARY OF CHANGES, AMENDMENT 1

Table 6 describes the changes made in Amendment 1 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), in the table of contents, in the list of abbreviations and definitions of terms, and in the synopsis are not listed.

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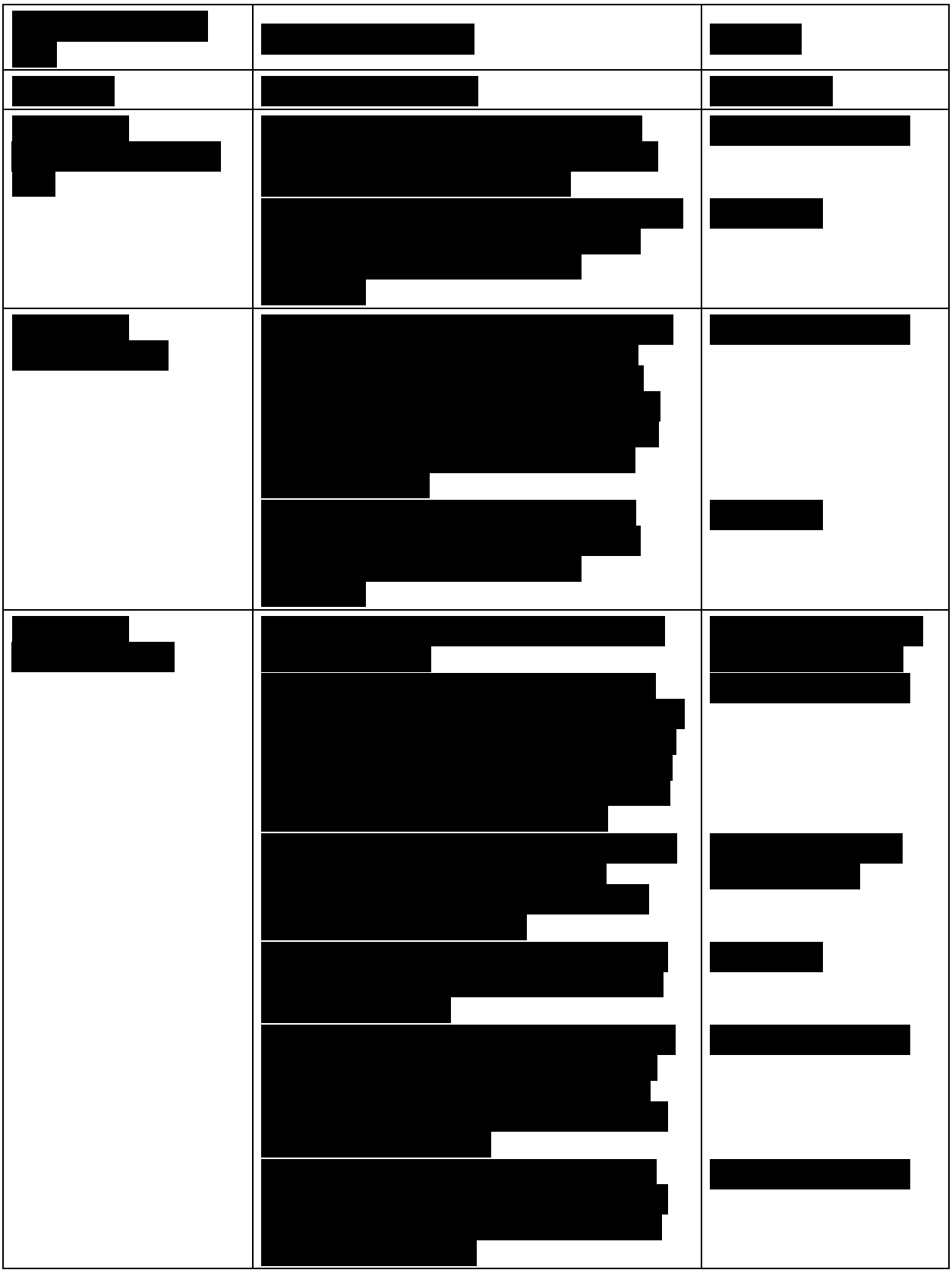

Section Number and Title	Description of Change	Rationale
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1. INTRODUCTION

1.1. Background Information and Study Rationale

Prader-Willi syndrome (PWS) is a rare complex genetic disorder characterized by a myriad of symptoms including short stature, hypotonia, hyperphagia, early onset childhood obesity, hypogonadism, behavioral problems, excessive daytime sleepiness (EDS), and cognitive dysfunction (Holm et al 1993). The disease is due to deletion of paternal copies of imprinted genes at chromosomal region 15q11.2-q13 (65 to 75% of individuals), maternal uniparental disomy 15 (20 to 30%), or an imprinting defect (1 to 3%) (Cassidy et al 2012; Driscoll et al 2017).

In addition to genetic defects, neuroanatomical abnormalities have been found in the postmortem hypothalamus in patients with PWS, and many of the clinical manifestations of PWS are associated with or have been hypothesized to arise from hypothalamic dysfunction (Hertz et al 1993; Swaab et al 1995; Vgontzas et al 1996; Swaab 1997; Manni et al 2001; Goldstone et al 2008). Notably, the hypothalamus is a crucial brain region for regulating sleep-wake timing and stability (Scammell et al 2017; España and Scammell 2011; Saper et al 2005), as well as hunger/satiety (Bruni et al 2010). Additionally, structural brain defects identified in imaging studies are increasingly being recognized as contributing to cognitive and behavioral problems that are characteristic of patients with PWS (Miller et al 2006).

Excessive daytime sleepiness is prevalent in this population; studies show 50 to 100% of patients with PWS have EDS, based on subjective (parent/caregiver reports) and/or objective (multiple sleep latency test [MSLT]) measures (Camfferman et al 2008). The impact of EDS on the severity of PWS has been recognized as being underappreciated, and there is an unmet need for effective treatments to address EDS in patients with PWS (Camfferman et al 2008). Patients with PWS have a tendency to wake early, which could be related to underlying behavioral problems associated with the disease, such as anxiety, compulsive behavior, and depression (Richdale et al 1999; Bingeliene et al 2015; Clarke et al 1989). Importantly, EDS appears to be continuously present across a patient's lifetime (Angriman et al 2015).

WAKIX® (pitolisant) is currently approved in the United States (US) for the treatment of EDS or cataplexy in adult patients with narcolepsy and in the European Union (EU) for the treatment of narcolepsy with or without cataplexy in adults. Pitolisant is also approved for narcolepsy in multiple other countries.

Pitolisant is a potent and highly selective histamine 3 (H_3) receptor antagonist/inverse agonist with a novel mechanism of action. It triggers activation of histaminergic neurons in the brain, a neuronal system involved in the maintenance of wakefulness, attention, and cognition. Pitolisant binds to H_3 receptors and blocks the normal negative feedback mechanism for histamine synthesis and release. It also functions as an inverse agonist, resulting in enhanced histamine synthesis and release from presynaptic neurons.

Pitolisant easily crosses the blood-brain barrier so that after low oral doses it elicits histamine release in the central nervous system. It also increases the release of other wake-promoting neurotransmitters (dopamine, noradrenaline, serotonin, and acetylcholine) via heteroreceptors within those neuronal systems. Importantly, pitolisant does not increase dopamine release in the

striatum, including the nucleus accumbens, which differentiates pitolisant from other wake-promoting agents that have abuse liability, such as amphetamines.

In patients with narcolepsy, loss of hypocretin signaling destabilizes sleep-wake states, resulting in frequent shifts between sleep and wakefulness. Pitolisant is hypothesized to compensate for the hypocretin deficiency by binding to H_3 receptors, which increases histaminergic transmission in the brain, helping to stabilize states of sleep and wakefulness.

Although patients with PWS exhibit narcolepsy-like symptoms, the sleep abnormalities in PWS are different from those of narcolepsy (Esbensen and Schwichtenberg 2016). Narcolepsy type 1 is characterized by EDS plus cataplexy; most people with PWS have chronic sleepiness and about 20% have brief episodes of muscle weakness suggestive of cataplexy (Tobias et al 2002; Weselake et al 2014). As in people with narcolepsy, patients with PWS have poor regulation of rapid eye movement (REM) sleep with abnormal REM sleep cycles, sleep onset REM periods, more episodes of REM sleep, and variable REM latency (Hertz et al 1993; Vgontzas et al 1996; Priano et al 2006; Camfferman et al 2008). In narcolepsy type 1 (with cataplexy), cerebrospinal fluid (CSF) hypocretin level is usually very low (≤110 pg/mL), and some people with PWS have moderately low CSF hypocretin levels (192 pg/mL on average compared to about 320 pg/mL in controls). In contrast to narcolepsy, sleep paralysis and hypnagogic/hypnopompic hallucinations are uncommon in PWS (Ghergan et al 2017). Also, the genetic markers associated with narcolepsy (e.g., variations in the human leukocyte antigen complex) are not associated with PWS (Camfferman et al 2008; Manni et al 2001).

Given the role of the hypothalamus in PWS, the role of hypocretin in sleep-wake state stability, and the potential synergy between hypocretin and histamine signaling in the brain, there is a scientific rationale as to why pitolisant may improve EDS in patients with PWS.

1.2. Rationale for Study Design

This Phase 2 randomized, double-blind, placebo-controlled, proof of concept (POC) study with an optional Open-Label Extension (OLE) will evaluate the safety and efficacy of pitolisant compared with placebo in the treatment of EDS and other symptoms (including behavioral problems and cognition) in patients with PWS ages 6 to 65 years. In addition, this study will evaluate the effect of treatment with pitolisant compared with placebo on the perceived caregiver burden with these patients.

In the randomized Double-Blind Treatment Phase, investigators, patients, and their caregivers/parent(s)/legal guardian(s) will be blinded to treatment assignment, which will minimize the potential bias in safety and efficacy assessments. The OLE Phase will allow for eligible patients (regardless of their treatment assignment in the Double-Blind Treatment Phase) to receive pitolisant until the Sponsor elects to terminate the study. The OLE will also allow for the assessment of long-term safety and effectiveness of pitolisant in this patient population.

Approximately 60 eligible patients ages 6 to 65 years will be enrolled in the study and will be randomized 1:1:1 by treatment (20 patients at a lower dose of pitolisant, 20 patients at a higher dose of pitolisant, and 20 patients on placebo) in the Double-Blind Treatment Phase. In the OLE Phase, [redacted] The inclusion of pediatric patients in the study was based on the manifestation of the syndrome in early childhood, and the minimum enrollment age of 6 years was selected based on pediatric data for pitolisant that are available to

date. The maximum age of 65 years allows for a representative proportion of each patient age group with PWS.

The primary efficacy endpoint of change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for pitolisant compared with placebo was selected because EDS is prevalent in the PWS population, EDS has a significant impact on the daily lives of patients with PWS and their families, and pitolisant is FDA-approved for the treatment of EDS in adult patients with narcolepsy. To assess EDS, the ESS-CHAD (parent/caregiver version), a parent/caregiver-rated impression of the patient's level of daytime sleepiness, will be utilized.

The original Epworth Sleepiness Scale (ESS) is a validated measure with high specificity and sensitivity for assessing subjective sleepiness in adults with sleep disorders (Johns 1991). The ESS was used as the primary subjective measure of EDS in controlled clinical trials that supported FDA approval of modafinil, armodafinil, sodium oxybate, and pitolisant for EDS in patients with narcolepsy. The measure also supported the approval of pitolisant for narcolepsy in the EU. The ESS-CHAD is a modified version of the ESS, with minor changes to make the questionnaire more appropriate for adolescents and younger children; the instructions are easier to comprehend, and the descriptions of activities are more applicable to children and adolescents (Johns 2015). The ESS-CHAD has been shown to be a valid, reliable, and unidimensional measure of daytime sleepiness in adolescents 12 to <18 years old (Janssen et al 2017). Most children ≥9 years old and most adolescents can answer the ESS-CHAD without assistance, whereas younger children may require parental assistance. In this study, the ESS-CHAD parent/caregiver version will be used. Because PWS is a neurodevelopmental disorder, with approximately 30 to 40% of patients who also have autism spectrum disorder, it is expected that the parent/caregiver will be able to provide the most reliable information regarding the patient's degree of EDS. The questionnaire will be administered to the parent/caregiver, who will answer questions regarding the patient's likelihood of falling asleep during specified activities (Section 6.3.1).

Key secondary efficacy endpoints of caregiver-rated impression of severity of the patient's symptoms of EDS and clinician-rated impression of the severity of the patient's overall clinical status will be evaluated using caregiver and clinical global impression scales. The Caregiver Global Impression of Severity (CaGI-S) will be assessed at every study visit and will evaluate the caregiver's impression of the patient's symptoms of EDS over the past week (Section 6.3.1). The Clinical Global Impression of Severity (CGI-S) will also be assessed at every study visit and will evaluate the clinician's overall assessment of the severity of the patient's current overall clinical status related to PWS based on his/her experience with this patient population (Section 6.3.3). The scales were chosen in order to minimize recall bias as the caregiver or clinician is not required to relate his/her rating of the patient's symptoms to a baseline score.

Other secondary efficacy endpoints of changes from Baseline to Week 11 in behavior and cognition and changes in perceived caregiver burden for pitolisant compared with placebo were selected to investigate the impact of pitolisant on other symptoms of PWS. The following provides brief descriptions of the scales and questionnaires to be used to evaluate these endpoints, with additional details presented in Section 6.3:

- The Aberrant Behavior Checklist-Community, Second Edition (ABC-C) (Section 6.3.4): The ABC-C covers a wide range of symptoms and is commonly used to assess problematic behavior at home, in educational and work settings, and in

residential and community-based facilities. This second edition of the checklist incorporates >30 years of research, including extensive data on validity, reliability, and documentation of intervention effects.

- The Montefiore-Einstein Rigidity Scale –Revised for Research Studies in PWS (MERS-R-PWS) will be used to evaluate rigidity, a core behavioral feature of patients with PWS (Section 6.3.5). The MERS-R-PWS, developed by Dr. B Taylor and Dr. E Hollander, is an adaptation of the Montefiore-Einstein Rigidity Scale-Revised (MERS-R), which was developed in response to the limitations of available outcome measures to evaluate rigid behaviors in patient populations (Hollander 2016). For example, scales commonly used to measure repetitive behaviors in other conditions (e.g., the Children's Yale-Brown Obsessive Compulsive Scale and the Repetitive Behavior Scale-Revised) are either non-specific (do not specifically focus on rigidity) or overly specific (use very specific examples of rigid behaviors but omit others). In collaboration with parents of children with PWS and the PWS Clinical Trials Consortium Behavioral Biomarker Working Group, the MERS-R was revised to evaluate rigid behaviors in children and adults with PWS in research studies (MERS-R-PWS). The MERS-R-PWS is a clinician-rated, semi-structured interview conducted with both the patient with PWS and their caregiver present. The scale measures three domains of rigid behavior (behavioral rigidity, cognitive rigidity, and protest) that result from a real or perceived interruption to rigidity. The MERS-R-PWS is currently being used as a secondary outcome measure in a US Food and Drug Administration (FDA)-funded study (ClinicalTrials.gov Identifier: NCT03197662) examining the efficacy of oxytocin in a double-blind, randomized, placebo-controlled 8-week trial of 50 children with PWS and in a Phase 2 study (ClinicalTrials.gov Identifier: NCT03848481) examining the efficacy of cannabidivarin in a double-blind, randomized, placebo-controlled trial of 26 individuals with PWS.
- The Cogstate Computerized Cognitive Test Battery evaluates cognition and changes in cognition (Section 6.3.6). Peer reviewed publications have examined the clinical utility and psychometric properties of the Cogstate test battery and have demonstrated its validity and reliability in assessing cognitive function in children and adults in various indications, e.g., attention deficit hyperactivity disorder, mild cognitive impairment, concussion, fatigue, alcohol use, and cognitive effects of various medications (Mollica et al 2004; Maruff et al 2004; Collie et al 2003; Falleti et al 2003; Collie et al 2006; Maruff et al 2006).
- The 22-item Zarit Burden Interview (ZBI-22) (Zarit and Zarit 1990) is a widely accepted and frequently used instrument to assess the psychosocial and health toll of being the caregiver for an individual with a disability or chronic illness (Section 6.3.7). The measure has been shown to have good internal consistency, content validity, and reliability, and in a study by Kayadjanian et al (2018), ZBI-22 was shown to be a good predictor of the impact of PWS on many aspects of the caregiver's quality of life.
- Hyperphagia in patients with PWS will be evaluated as an exploratory endpoint using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) in conjunction with the

Food Safe Zone Questionnaire (FSZQ). Serum levels of ghrelin (acylated and unacylated) will also be evaluated.

- Changes in hyperphagia will be assessed using the HQ-CT (Section 6.3.8). The HQ-CT measures food-related preoccupations and problems as well as the severity of these concerns, focusing on food-seeking behaviors common among patients with PWS (Dykens et al 2007; Fehnel et al 2015). The severity items scale is based on the definition of symptom-related impairment per the American Psychiatric Association, and this questionnaire has been used in more than 10 studies and clinical trials in PWS and is recognized by the FDA as reliable and sensitive to treatment effects in patients with PWS. In conjunction with the HQ-CT, the FSZQ (Section 6.3.9) will be used to assess environmental controls that are in place to manage hyperphagia in patients with PWS. The FSZQ was developed by Elizabeth Roof (Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN) to assess strategies developed by caregivers to control food behaviors. The questionnaire was developed based on the input of caregivers and has been tested in over 300 parents with children with PWS and in adults with PWS and is currently being used in four ongoing clinical trials in PWS.
- The appetite-stimulating hormone ghrelin is produced by ghrelinergic cells in the gut and acts as a peripheral orexigenic signal that communicates with the arcuate nucleus of the hypothalamus to increase appetite and food intake in response to fasting (Khan et al 2018). In healthy individuals, fasting promotes increased secretion of ghrelin in the gut, and levels decrease after eating; however, this does not occur in patients with PWS. Children and adults with PWS have between 3.0- and 4.5-fold higher fasting plasma levels of ghrelin compared with matched control patients with obesity (Cummings et al 2002; DelParigi et al 2002; Haqq et al 2003), and ghrelin levels may influence eating behavior in these patients (Allas et al 2018). The mechanism underlying ghrelin dysregulation and the functional impact of elevated ghrelin levels on symptoms of PWS, including hyperphagia, are currently unknown; however, a link between ghrelin and the histaminergic system has been suggested by studies investigating the gastroprotective role of ghrelin in the gut (Adami et al 2010). In this study, serum ghrelin levels (acylated and unacylated) will be evaluated (Section 6.3.10).

Standard safety and tolerability assessments will include adverse event (AE) monitoring, clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and suicidality. In addition, anxiety will be assessed using the Anxiety, Depression, and Mood Scale (ADAMS), and the frequency, type, and duration of seizures in patients with a history of seizure disorder will be collected (Section 6.5.6).

Characterization of the pharmacokinetics (PK) of pitolisant will inform the optimal dose selection strategy. Pitolisant is primarily metabolized by cytochrome P450 (CYP) 2D6 and to a lesser extent by CYP3A4; metabolites are further metabolized or conjugated with glycine or glucuronic acid. None of the pitolisant metabolites are pharmacologically active. BP1.3484 is the most predominant metabolite after repeat dosing with pitolisant, and PK analyses in this study will include evaluation of this major metabolite.

1.3. Dose Rationale

[redacted]

1.3.1. Age-Based Dosing [redacted]

Eligible patients (60 in total) will be randomized at a 1:1:1 ratio to one of three treatment groups: higher dose pitolisant, lower dose pitolisant, or placebo (20 patients per group).

The doses for each age range (Table 8) were selected based on safety and efficacy data from the clinical development program for adults with narcolepsy and PK data from 24 pediatric patients with narcolepsy (ages 7 to <18 years) receiving a single dose of pitolisant. The pitolisant dose for adult patients is consistent with the FDA-approved United States Prescribing Information (USPI). The pediatric age-based doses were chosen based on modeling using the PK data available from the 24 pediatric patients with narcolepsy, which suggest that pediatric patients have higher exposure to pitolisant than adults. The titration period is consistent with the FDA-approved United States Prescribing Information (USPI).

1.3.2. [redacted] Dosing (OLE Phase After Implementation of Protocol Amendment 6)

The [redacted] dosing regimens (Table 9) were selected based on:

- Efficacy signals that were observed for the higher dose pitolisant treatment group in the completed Double-Blind Treatment Phase of this study, suggesting a target for [redacted] dosing of approximately [redacted] mg/kg.
- Population PK simulations:
  - Area under the curve during a dosing interval at steady state (AUC_{tau}) and maximum observed concentration (C_{max}) in patients with PWS receiving the [redacted] dosing regimens were similar to those in patients with narcolepsy receiving the doses included in the FDA-approved prescribing information for WAKIX (pitolisant).
  - The estimated risk of QT interval prolongation in patients with PWS using the [redacted] dosing regimens described in Table 9 is consistent with the risk described in patients with narcolepsy in the FDA-approved prescribing information for WAKIX (pitolisant).
- Safety data:
  - Pitolisant is well tolerated in adult and pediatric patients with narcolepsy and in ongoing clinical development programs at doses up to 35.6 mg once daily.
  - Pitolisant is well tolerated in adult and pediatric patients with PWS at doses up to 35.6 mg in the Double-Blind Treatment Phase of this study and up to [redacted] mg in studies HBS-101-CL-003 and HBS-101-CL-004.

- The safety/tolerability profile of pitolisant in pediatric patients is generally consistent with the established safety/tolerability profile in adult patients.
- No dose-related adverse effects were identified in the pooled narcolepsy New Drug Application (NDA) safety population of 1513 patients who received pitolisant 17.8 mg or 35.6 mg once daily for a mean of 33 weeks.

During the OLE Phase, pitolisant dose can be adjusted (higher or lower) based on Investigator discretion (Section 3.1.5.2).

1.4. Potential Risks and Benefits

The overall safety/tolerability profile of pitolisant at doses of 4.45 to 35.6 mg once daily has been well characterized from 41 completed studies. Of the 41 completed studies, 19 were Phase 1 studies and 22 were Phase 2/3 studies in the indications of narcolepsy, obstructive sleep apnea, Parkinson's disease, epilepsy, schizophrenia, Lewy body dementia, and attention deficit hyperactivity disorder (i.e., 8 narcolepsy and 14 non narcolepsy studies). The Phase 2/3 data comprised a total of 1513 patients who were treated with pitolisant; 1043 of these patients received pitolisant in double-blind, placebo-controlled studies. The most frequently reported (≥5%) treatment-emergent AEs (TEAEs) in patients who received pitolisant in the Phase 2/3 studies were headache (13.5%), insomnia (8.5%), and nausea (5.8%); the majority of these events were considered treatment-related.

Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment. Pitolisant prolongs the QT interval. The use of pitolisant should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Pitolisant is contraindicated in patients with severe hepatic impairment and is not recommended in patients with end-stage renal disease.

In the clinical development program for pitolisant, there was no evidence of withdrawal syndrome from pitolisant or rebound effect upon discontinuation of therapy, and long-term studies did not demonstrate evidence of the development of tolerance to pitolisant. There were no clinically relevant effects of pitolisant on vital signs, electrocardiographic parameters, or laboratory findings across the database of patients exposed to pitolisant.

Additional information is provided in the WAKIX (pitolisant) Investigator's Brochure (IB) and current prescribing information for WAKIX (pitolisant).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of pitolisant compared with placebo in treating EDS in patients with PWS ages 6 to 65 years.

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

The key secondary objectives of this study are 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.

2.2.2. 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 functions
- Change in caregiver burden
- Effectiveness of pitolisant during long-term treatment

2.3. 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 ghrelin levels
- The PK of pitolisant and its major metabolite, BP1.3484
- The relationship between levels of pitolisant (PK) and treatment effect (pharmacodynamics)

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group, Phase 2 POC 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 Titration Period and an 8-week Stable Dose Period), and an optional OLE Phase. The OLE Phase will be multi-year in duration and will continue until the Sponsor elects to terminate the study. An overall schema of the study design is provided in Figure 1.

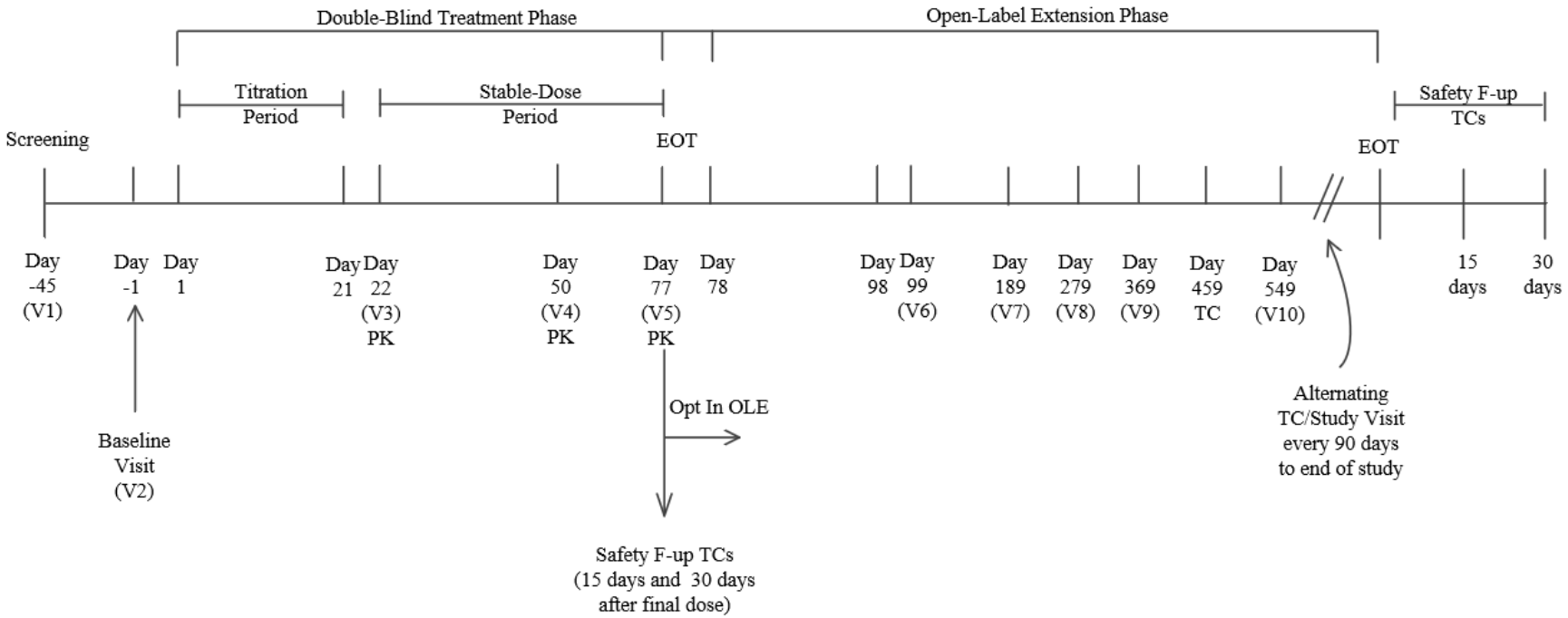
During Screening, patients who meet all eligibility criteria will be enrolled in the study, randomized in a 1:1:1 ratio to receive treatment with lower dose pitolisant, higher dose pitolisant, or matching placebo (20 patients per treatment group, ages 6 to 65 years) (Section 3.1.2). The lower and higher 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. In the Double-Blind Treatment Phase, patients will be titrated to their randomized stable dose of study drug during the Titration Period (Section 3.1.3). After completion of the Titration Period, patients will continue to take study drug at their randomized stable dose once daily in the morning upon wakening for an additional 8 weeks of blinded treatment (Stable Dose Period). The duration of the Double-Blind Treatment Phase will be 11 weeks.

Eligible patients who complete the Double-Blind Treatment Phase will be given the opportunity to participate in an optional OLE Phase.

In the OLE Phase, prior to implementation of Amendment 6, patients received a maximum target dose of pitolisant 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; Section 3.1.4). [redacted]

Safety, efficacy, and PK will be evaluated as detailed in Section 3.1.3 (Double-Blind Treatment Phase) and Section 3.1.4 (OLE Phase).

Figure 1: Overall Study Design



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

3.1.2. Screening and Baseline Visits

At the Screening Visit (Visit 1), after written informed consent/assent is provided, patients will complete screening assessments and will be provided with a sleep diary to measure daily sleep activity. Specific procedures and assessments for the Screening Visit (Visit 1) may be conducted remotely as detailed in Section 6.6.1.

The sleep diary is to be completed daily for 14 days (minimum of 7 days required for evaluation); patients will record (with the assistance of their caregiver if needed) the time they go to bed each evening and the time they wake up each morning (an example of the study diary, which includes a sleep diary section and a study drug dosing section, is provided in Appendix B). The patient will return the sleep diary to the site at the end of the 14-day period.

To be eligible for the study, patients must have a minimum of 7 evaluable nights from the 14 nights of sleep diary data. Using the patient-recorded times, a qualified study team member will calculate the evaluable hours and minutes the patient slept per night. Using all evaluable nights, the mean subjective total sleep time (sTST) per night must be at least 8 hours for patients ages 6 to <12 years, at least 7 hours for patients 12 to <18 years, or at least 6 hours for patients ≥18 years.

At the Baseline Visit (Visit 2), patients who continue to meet all eligibility criteria based on their screening sleep diary will be randomized at a 1:1:1 ratio to receive once daily treatment with lower dose pitolisant, higher dose pitolisant, or matching placebo in the Double-Blind Treatment Phase (Section 3.1.3). Patients will not be stratified by age.

The stable doses of pitolisant (lower or higher) in the Double-Blind Treatment Phase are:

- 8.9 mg or 17.8 mg pitolisant in children ages 6 to <12 years
- 13.35 mg or 26.7 mg pitolisant in adolescents ages 12 to <18 years
- 17.8 mg or 35.6 mg pitolisant in adults ages 18 to 65 years

If the Screening Visit (Visit 1) was conducted remotely, refer to Section 6.6.1 for the procedures that will be conducted at the Baseline Visit (Visit 2).

After completion of all Baseline assessments eligible patients will be dispensed study drug at the Baseline Visit (Day -1) and will be instructed to take study drug once daily, beginning the following morning upon wakening (Day 1) in accordance with the schedule presented in Table 7. Patients will be instructed to record daily the number of tablets administered (and from which bottle) in the study drug dosing section of the study diary (with the assistance of their caregiver if needed). The study diary will be used in the Double-Blind Treatment Phase only (an example of the study diary is provided in Appendix B).

Study drug administration should begin in the morning on the day after the Baseline Visit; the first day of study drug administration is Day 1.

Patients who fail screening for any reason (e.g., sleep diary, laboratory test) may be rescreened once at the discretion of the Investigator.

3.1.3. Double-Blind Treatment Phase

The day after the Baseline Visit, patients will take their first dose of study drug in the 3-week Titration Period (Day 1) (Figure 1). Patients will be titrated to their randomized stable dose of study drug in accordance with the schedule presented in Table 7; study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized stable dose, per Table 7), with all patients at their randomized stable dose by Day 15 of the Titration Period. At the end of the 3-week Titration Period, patients will continue to take study drug (pitolisant or placebo) in accordance with their randomized stable dose once daily in the morning upon wakening for an additional 8 weeks (Stable Dose Period; Days 22 to 77) for a total of 11 weeks of double-blind treatment.

Table 7: Study Drug Dosing in the Double-Blind Treatment Phase

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)				
Lower dose pitolisant	4.45 mg	8.9 mg	8.9 mg	8.9 mg
Higher 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)				
Lower dose pitolisant	4.45 mg	8.9 mg	13.35 mg	13.35 mg
Higher 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)				
Lower dose pitolisant	4.45 mg	8.9 mg	17.8 mg	17.8 mg
Higher 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.

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.

Patients and/or their caregivers will receive telephone calls (TCs) from the study site on Days 8 and 15 (±3 days) (TCs 1 and 2, respectively) during the 3-week Titration Period to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug dose. During the 8-week Stable Dose Period, patients will complete safety, efficacy, and PK assessments at the study site on Day 22 (Visit 3), Day 50 (Visit 4), and Day 77 (Visit 5) (window for Visits 3, 4, and 5 is ±3 days), and patients and/or their caregivers will receive TCs

from the study site on Days 29, 36, and 57 (±3 days) to assess for AEs and concomitant medication use, complete the C-SSRS and ADAMS, and confirm study drug dose.

At the end of the Double-Blind Treatment Phase, eligible patients will be given the opportunity to enter an optional OLE Phase (Section 3.1.4). If a patient does not enter the OLE Phase, the patient 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 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 use of concomitant medications and to complete the C-SSRS and ADAMS (Section 7.5).

3.1.4. Open-Label Extension Phase

Before patients can enter the OLE Phase of the study, eligibility criteria must be confirmed at Visit 5 in the Double-Blind Treatment Phase.

Patients who discontinue early from the Double-Blind Treatment Phase of the study but wish to enter the OLE Phase will require approval from the Medical Monitor in consultation with the Investigator (eligibility criteria must be confirmed).

In the OLE Phase, prior to implementation of Amendment 6, patients received a maximum target dose of pitolisant 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) as detailed in Table 8.

[redacted]

Adjustments to pitolisant dose are permitted in the OLE Phase. Details for pitolisant dose adjustments are provided in Section 3.1.5.2.

Eligible patients will be dispensed open-label pitolisant at Visit 5 (Day 77 ±3 days) of the Double-Blind Treatment Phase and will take their first dose of open-label pitolisant in the morning the following day (Day 78 ±3 days). Patients will continue to take open-label pitolisant once daily in the morning upon wakening through the end of the study.

Table 8: Pitolisant Dosing in the Open-Label Extension Phase [redacted]

Age Groups	Titration Period (3 Weeks)			Long-Term Dosing Period
	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

EOT = End of Treatment; OLE = Open-Label Extension

Patients and/or their caregivers will receive TCs from the study site on Days 85 and 92 (±3 days) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm pitolisant dose titration. Patients and their caregivers will complete safety and effectiveness assessments on Day 99 (±3 days; Visit 6) and approximately every 90 days (±7 days) thereafter up to Day 369 (i.e., Days 189 [Visit 7], 279 [Visit 8], and 369 [Visit 9]).

After completion of Visit 9, patients and/or their caregivers will be contacted by telephone on Day 459 (±7 days; TC 8), after which patients and their caregivers will return for an on-site study visit on Day 549 (±7 days; Visit 10). This pattern of alternating TCs and on-site study visits approximately every 3 months will be repeated until either the patient withdraws from the study, or the study is terminated by the Sponsor. 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. At the TCs, AEs and concomitant medications will be recorded, the C-SSRS will be completed, and the current dose of pitolisant and receipt of study drug shipments will be confirmed (Section 7.4.2.2). Safety, effectiveness, and study drug compliance will be assessed at the on-site study visits as detailed in Section 7.4.2.3. All patients will complete an End of Treatment (EOT) Visit as outlined in Section 7.4.2.4.

Patients and/or their caregivers will receive Safety Follow-up TCs from the study site 15 days (±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 use of concomitant medication and to complete the ADAMS (Section 7.5).

3.1.5. Dose Adjustments

3.1.5.1. Double-Blind Treatment Phase

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

3.1.5.2. Open-Label Extension Phase

Adjustments in pitolisant dose are permitted in the OLE Phase.

Prior to implementation of Amendment 6, pitolisant doses could be adjusted (higher or lower) in 4.45 mg increments based on Investigator assessment of clinical response, tolerability and/or patient age.

After implementation of Amendment 6, pitolisant dose may be adjusted (higher or lower) based on Investigator discretion in consultation with the Medical Monitor up to the maximum daily dose allowed [redacted] (Table 9).

In the event a patient develops moderate hepatic impairment (Child-Pugh B) or moderate or severe renal impairment during the study, the dose of pitolisant may need to be decreased by the Investigator in consultation with the Medical Monitor. Patients who develop either end-stage renal disease (estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C) must be withdrawn from the study (Section 4.4.1).

If a patient began taking a strong CYP2D6 inhibitor during the OLE Phase, prior to implementation of Amendment 6, pitolisant dose was to be reduced by one half of the maximum age-based dose (Table 8). [redacted] If a patient begins taking a strong CYP3A4 inducer during the OLE Phase, pitolisant dose may be increased up to the maximum permitted daily dose based on the patient's age (prior to implementation of Amendment 6) [redacted].

3.1.6. Dose Interruptions

Every effort should be made to educate patients/caregivers/parent(s)/legal guardian(s) on the importance of remaining compliant with study drug dosing.

No interruptions in study drug dosing are expected in the Double-Blind Treatment Phase of the study. If a dose is missed in the Double-Blind Treatment Phase, the patient should take the next dose the following morning upon wakening. If dosing is interrupted (e.g., due to an AE) for 7 or more days, consult with the Medical Monitor before restarting study drug.

In the OLE Phase of the study, interruptions in study drug dosing are permitted based on tolerability and the discretion of the Investigator. If a dose is missed in the OLE Phase, the patient should take the next dose the following morning upon wakening.

If a patient is taking a pitolisant dose that is >8.9 mg and has a dosing interruption exceeding 7 days in the OLE Phase, before restarting study drug, the Investigator should consult with the Medical Monitor.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Double-Blind Treatment Phase

3.2.1.1.1. Primary Efficacy Endpoint

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

3.2.1.1.2. Key Secondary Efficacy Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- CaGI-S for EDS
- CGI-S for overall clinical status related to PWS

3.2.1.1.3. Other Secondary Efficacy Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- Behavior as measured by the ABC-C
- Behavioral and cognitive rigidity as measured by the MERS-R-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

3.2.1.1.4. Exploratory Endpoints

Change from Baseline to Week 11 for pitolisant compared with placebo in:

- Total score of the HQ-CT in conjunction with the FSZQ
- Acylated and unacylated ghrelin levels

3.2.1.2. Open-Label Extension Phase

Long-term effectiveness of pitolisant as measured by ESS-CHAD (parent/caregiver version), CaGI-S for EDS, CGI-S for overall clinical status related to PWS, ABC-C, MERS-R-PWS, Cogstate Detection Test, Cogstate Identification Test, Cogstate One Back Test, ZBI-22, and HQ-CT in conjunction with the FSZQ will be assessed during the patient's first year of participation in the OLE Phase of the study. After the first year of participation, effectiveness measures will include the ESS-CHAD (parent/caregiver version) as reported by caregivers, CaGI-S, and CGI-S.

3.2.2. Pharmacokinetic and Pharmacodynamic Endpoints

- C_{max} of pitolisant and its major metabolite, BP1.3484

- Area under the concentration-time curve from time 0 to the last collection time (AUC_{last}) after administration of pitolisant
- Time to observed maximum concentration (t_{max}) of pitolisant
- Exposure-response relationship between pitolisant levels and change in efficacy measures

3.2.3. Safety Endpoints

Safety will be assessed by monitoring the incidence of AEs and changes in clinical laboratory test results, vital signs, and 12-lead ECG results, along with additional safety assessments (suicidality, anxiety, and monitoring of seizures in patients with seizure disorder) from Baseline to Week 11 in the Double-Blind Treatment Phase and from Baseline to study completion in the OLE Phase.

3.3. Study Duration

The study is expected to be multi-year in duration. The Double-Blind Treatment Phase will remain open until the last patient completes this phase of the study, and the OLE Phase will remain open until the Sponsor elects to terminate the study.

The duration of participation for individual patients in the Double-Blind Treatment Phase is expected to be up to approximately 21 weeks, including a maximum of 45 days of screening, 11 weeks of double-blind treatment (includes a 3-week Titration Period and an 8-week Stable Dose Period), and 30 days of safety follow-up for patients who do not enter the optional OLE Phase of the study. For patients who enter the OLE Phase of the study, individual patient participation is expected to be multi-year in duration.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 60 patients with PWS are planned to be enrolled in the study at approximately 10 sites in the US.

4.1.1. Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is able to provide voluntary, written informed consent (patient or parent[s]/legal guardian[s]) and, where applicable, voluntary, written assent (patient, as appropriate).
2. Has a diagnosis of PWS confirmed by genetic testing and patient medical records. Genetic testing will be provided by the Sponsor, if not confirmed based on the review of the patient's medical records.
3. Male or female patients ages 6 to 65 years at the time of enrollment.
4. Demonstrates adequate sleep duration via patient sleep diary during Screening defined as at least 8 hours of sleep per night for patients ages 6 to <12 years, at least 7 hours for patients ages 12 to <18 years, or at least 6 hours for patients ages ≥18 years, based on the mean number of hours from up to 14 nights (at least 7 nights must be recorded for evaluation).
5. Has EDS as determined by ESS-CHAD (parent/caregiver version) score ≥12.
6. If taking hormone treatments (including growth hormone, testosterone, and estrogen supplements) and/or allowed chronic concomitant medication or supplements, patient must be on a stable dose of these medications for 3 months prior to randomization and for the duration of the Double-Blind Treatment Phase of the study; 10% variability in hormone dose is allowed.
7. If taking a wake-promoting treatment that could affect EDS (including stimulants, modafinil, and armodafinil), must be on a stable dose for at least 28 days prior to Screening and remain on a stable dose during the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.
8. If taking a chronically administered sedating medication for management of behavioral manifestations (e.g., hypnotics, benzodiazepines, antipsychotics, alpha agonists, anticholinergics, and antidepressants) must be on a stable dose for at least 28 days prior to Screening and remain on a stable dose during the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.
9. If using cannabidiol and/or tetrahydrocannabinol, patient must be on a stable dose for 28 days prior to randomization and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase).

10. If taking oxytocin or carbetocin, patient must be on a stable dose during the 28 days prior to randomization and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase) or agree to wash out of treatment for 5 half-lives or 14 days, whichever is longer.
11. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Baseline Visit and agree to remain abstinent or use an effective method of nonhormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
12. Has a consistent caregiver (preferably the same person throughout the Double-Blind Treatment Phase of the study) who is willing and able to complete the required assessments.
13. In the opinion of the Investigator, patient/parent(s)/legal guardian(s) is capable of understanding and complying with the requirements of the protocol and administration of oral study drug.

4.1.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from enrollment in the study:

1. Has a diagnosis of another genetic or chromosomal disorder distinct from PWS.
2. Has untreated OSA or is at high risk for OSA based on medical history and clinical assessment; or, has another relevant underlying sleep disorder that in the opinion of the Investigator is the primary contributing factor to the patient's EDS.
3. Consistently consumes >600 mg of caffeine per day and is unable/unwilling to reduce caffeine intake to <600 mg per day for the duration of the Double-Blind Treatment Phase of the study; caffeine intake should remain consistent during Screening and throughout the Double-Blind Treatment Phase of the study.
4. Does not agree to discontinue any prohibited medication or substance listed in the protocol (Section 5.7.2).
5. Participation in an interventional research study involving another investigational medication or device in the 28 days prior to enrollment and for the duration of the Double-Blind Treatment Phase of the study, unless the Investigator consults with the Medical Monitor and obtains written approval for the patient to enroll; patients who complete a washout of an investigational medication of at least 5 half-lives or 14 days (whichever is longer) may be enrolled in the Double-Blind Treatment Phase of the study. Patients considering participation in another interventional research study in the OLE Phase must consult with the Investigator who will consult with the Medical Monitor.
6. Has a primary psychiatric diagnosis with current active symptoms of psychosis or schizophrenia.
7. Has a diagnosis of end-stage renal disease (eGFR of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).

8. Has a diagnosis of moderate or severe renal impairment (eGFR ≥15 to ≤59 mL/minute/1.73 m^2) or moderate hepatic impairment (Child-Pugh B) at Screening or during the Double-Blind Treatment Phase.
9. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.
10. Has a known history of long QT syndrome or any significant history of a serious abnormality of the ECG (e.g., recent myocardial infarction, clinically significant arrhythmia) or QT interval corrected for heart rate according to Fridericia's formula (QTcF) >442 ms for patients ages 0 to <10 years and >439 ms for patients ages 10 to <20 years, regardless of gender, and >450 ms for male patients and >470 ms for female patients ages 20 to 65 years (ECG QTcF = QT/3√ RR) (Mason et al 2007).
11. Has a family history of sudden/unexplained death, cardiac death, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member.
12. If receiving any new or initiating a change in allied health therapies or interventions for symptoms of PWS, must be on a stable course of therapy for at least 28 days prior to randomization.
13. Has a current or recent (within one year) history of a substance use disorder or dependence disorder, including alcohol and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).
14. Has planned surgery during the Double-Blind Treatment Phase of the study; planned surgery is permitted during the OLE Phase.
15. Is receiving a concomitant medication that is known to be a strong CYP2D6 inhibitor, a strong CYP3A4 inducer, or a centrally acting H_1 receptor antagonist; patients who complete a washout of these medications of at least 5 half-lives or 14 days (whichever is longer) can be enrolled in the Double-Blind Treatment Phase of the study. Use of strong CYP2D6 inhibitors and strong CYP3A4 inducers is allowed during the OLE Phase; however, adjustment of pitolisant dose is required (Section 5.7.3). Although not prohibited during the OLE Phase of the study, use of H_1 receptor antagonists should be avoided.
16. Is receiving a medication known to prolong the QT interval.
17. Has a significant risk of committing suicide based on history, routine psychiatric examination, Investigator's judgment, or who has an answer of "yes" on any question other than questions 1 to 3 on the Very Young Child/Cognitively Impaired-Lifetime Recent Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix L).
18. Has a history of seizures that have recently (within 6 months) been treated with antiepileptic medications that are strong CYP3A4 inducers. Patients with a history of seizures must have a stable seizure history (e.g., frequency and severity) for at least 6 months prior to enrollment.
19. Is currently breastfeeding or planning to breastfeed over the course of the study. Lactating women must agree not to breastfeed for the duration of the study (Double-Blind Treatment Phase and OLE Phase) and for 21 days after final dose of study drug.

20. Based on the judgment of the Investigator, patient is unsuitable for the study for any reason, including but not limited to unstable or uncontrolled medical conditions (including psychiatric and neurological conditions) or a medical condition that might interfere with the conduct of the study, confound interpretation of study results, pose a health risk to the patient, or compromise the integrity of the study.

4.2. Method of Assigning Patients to Treatment Groups

Patients who meet all eligibility criteria will be randomized to treatment and will be assigned a unique identification (ID) number prior to dosing using interactive response technology (IRT).

All randomization information will be kept in a secure location accessible only by the randomization personnel (e.g., study drug supplier) until the time of unblinding. No patient may receive study drug prior to being randomized in the study.

4.2.1. Procedures for Handling Randomized Patients Who Do Not Meet the Study Eligibility Criteria

Patients who fail to meet the eligibility criteria should not receive study drug. In the event a patient does not meet study eligibility criteria, but is enrolled and receives study drug, the Investigator should inform the Sponsor immediately. The Sponsor's Medical Monitor and the Investigator will determine whether to allow the patient to continue in the study.

For patients who opt to enter the OLE Phase of the study, entrance eligibility criteria must be confirmed before administration of open-label pitolisant.

4.3. Blinding

For the Double-Blind Treatment Phase of the study, patients, caregivers, parent(s)/legal guardian(s), Investigators, personnel involved in the conduct and interpretation of the study, site personnel involved in safety and efficacy assessments, and Sponsor staff will be blinded to the treatment assignments.

Patients are not receiving blinded study drug in the OLE Phase of the study; however, in the OLE Phase, patients, parents/caregivers, Investigators, personnel involved in the conduct and interpretation of the study, and site personnel involved in safety and efficacy assessments will remain blinded to a patient's treatment assignment in the Double-Blind Treatment Phase.

4.3.1. Breaking the Blind

The study blind should not be broken except in medical emergencies when the appropriate medical management of the patient requires knowledge of the study drug he/she received or to ensure patient safety in the trial. If it is necessary to unblind a patient's treatment assignment to manage medical treatment, unblinding will occur through the IRT system.

The Investigator should notify the Sponsor's Medical Monitor in a timely manner if unblinding is necessary. An attempt should be made to contact the Sponsor before breaking the blind.

All circumstances leading to premature unblinding must be clearly documented.

4.4. Patient Withdrawal and Follow-up

4.4.1. Patient Withdrawal

Patients are free to withdraw from the study at any time for any reason. A patient may also be withdrawn from the study by the Investigator or the Sponsor at any time for safety, behavioral, or administrative reasons if either determines that it is not in the patient's best interest to continue participation.

Possible reasons for early withdrawal include:

- AE
- Lack of effect
- Patient/parent(s)/legal guardian(s) decision
- Lost to follow-up
- No longer meets eligibility criteria
- Non-compliance with study protocol
- Non-compliance with study drug treatment
- Other, with specific reason (e.g., pregnancy)

Patients who develop end-stage renal disease (eGFR of <15 mL/minute/1.73 m^2), severe hepatic impairment (Child-Pugh C), or any other medical condition that in the opinion of the Investigator may pose a risk to the patient must be discontinued from the study.

The following ECG findings, based on the mean of triplicate 12-lead ECGs, require discontinuation from the study:

- Mean QTcF >500 ms
- Mean QTcF increase from Screening >60 ms AND mean QTcF >470 ms
- Heart rate increase from Baseline >65% or decrease from Baseline >40%

Any patient with a new positive response on question 4 (active suicidal ideation with some intent to act, without specific plan) and/or question 5 (active suicidal ideation with specific plan and intent) of the Very Young Child/Cognitively Impaired-Since Last Contact C-SSRS (Appendix M) will be discontinued and will require further evaluation by the Investigator.

The date and primary reason for early withdrawal will be recorded in the electronic case report form (eCRF). At the time of withdrawal from the study, every attempt should be made to complete the Early Termination (ET) Visit assessments (Section 7.3.3 and Section 7.4.3).

4.4.2. Temporary Interruption of Study Drug During the OLE Phase

As noted in Section 6.5.4, in the event of clinically significant ECG findings (other than those that require discontinuation of study drug treatment [Section 4.4.1]), in consultation with the Medical Monitor, the Investigator may decide to temporarily stop (interrupt) pitolisant dosing for 2 to 3 days. During this interruption, ECGs will be performed daily (locally or at the study site). Upon resolution of the ECG abnormality, pitolisant administration may resume at the same dose

as before the interruption, or the pitolisant dose may be lowered by 50%. If the condition persists after the interruption in dosing, the Investigator, in consultation with the Medical Monitor, will decide whether treatment should be permanently discontinued.

4.4.3. Procedures for Patient Follow-up

All patients who complete the Double-Blind Treatment Phase of the study are required to complete the safety assessments outlined in the EOT Visit (Section 7.3.2.4). Patients who prematurely discontinue study drug during the Double-Blind Treatment Phase are required to complete the safety assessments outlined in the ET Visit, and the reasons for discontinuation must be recorded (Section 7.3.3). Additionally, patients in the Double-Blind Treatment Phase who do not enter the OLE Phase will be contacted by telephone 15 days (±3 days) and 30 days (+3 days) after taking the final dose of blinded study drug 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 use of concomitant medication (Safety Follow-up TCs; Section 7.5).

All patients who complete the optional OLE Phase of the study are required to complete the safety assessments outlined in the EOT Visit (Section 7.4.2.4). Patients who prematurely discontinue study drug during the OLE Phase are required to complete the safety assessments outlined in the ET Visit, and the reasons for discontinuation must be recorded (Section 7.4.3). Additionally, patients in the OLE Phase will be contacted by telephone 15 (±3 days) and 30 days (+3 days) after taking the final dose of open-label study drug 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 use of concomitant medication (Safety Follow-up TCs; Section 7.5).

Every effort should be made to educate patients/caregivers/parent(s)/legal guardian(s) on the importance of remaining in the study and attending scheduled study visits, including those required after early discontinuation of study drug.

4.4.4. Withdrawal of Consent for Contact

Patients/parent(s)/legal guardian(s) who no longer wish to attend study visits will be asked if they may be contacted by telephone or other methods. However, if a patient/parent(s)/legal guardian(s) specifically withdraws consent to be contacted for additional information, no further study visits or study-related TCs will be conducted. For any patient who withdraws consent for contact, the Investigator will document the reason for withdrawal of consent in the eCRF.

4.4.5. Patients Deemed Lost to Follow-up

Investigators should make every effort to contact patients/parent(s)/legal guardian(s) who are potentially lost to follow-up, including pursuing any alternative contact methods permitted by local regulations or agreed by the patient/parent(s)/legal guardian(s). All attempts to contact the patient/parent(s)/legal guardian(s) will be documented in the patient's eCRF and source notes. At a minimum, three documented attempts to contact the patient/parent(s)/legal guardian(s), including at least one certified letter, should be performed before a patient is deemed lost to follow-up.

4.5. Patient Replacement

Patients who withdraw from the study will not be replaced. Patients who are randomized to treatment but withdraw prior to receiving any study drug may be replaced.

4.6. Study and Patient Completion

4.6.1. Study Completion

The Double-Blind Treatment Phase of the study will be completed when the last patient completes the EOT Visit after the final dose of blinded treatment.

The OLE Phase of the study will continue until the Sponsor elects to terminate the study.

4.6.2. Patient Completion

Patients who complete the EOT visit in the Double-Blind Treatment Phase will be considered to have completed the Double-Blind Treatment Phase. The OLE Phase of the study is optional and open-ended in duration.

4.7. Screen Failures

Patients who fail to meet eligibility criteria should not receive study drug.

Patients who fail to meet eligibility criteria at either the Screening or Baseline Visit will be screen-failed without receiving study drug. Patients may be rescreened at any point after failing any criterion, but only once for study entry.

If a patient is re-screened for enrollment, a new informed consent form (ICF) must be signed, and a new patient number will be assigned by IRT. If the patient is out of the initial 45-day screening window, all screening procedures must be repeated.

In the event a patient does not meet eligibility criteria, but is enrolled and receives study drug, the Investigator should inform the Sponsor immediately (Section 4.2.1).

5. STUDY TREATMENT

Study drug, defined as pitolisant (investigational product) or placebo (comparator), will be provided by the Sponsor. All patients should take their study drug once daily in the morning upon wakening. Dose adjustments are permitted in the OLE Phase of the study at the discretion of the Investigator as described in Section 3.1.5.2.

5.1. Description of Treatments

5.1.1. Pitolisant (Investigational Product)

Pitolisant tablets will be provided in strengths of 4.45 mg and 17.8 mg to accommodate the study doses:

- Pitolisant 4.45 mg tablets: white, round, plain, biconvex film-coated tablet, 3.7 mm in diameter. Each tablet contains 5 mg of pitolisant hydrochloride equivalent to 4.45 mg of pitolisant.
- Pitolisant 4.45 mg tablets: white, round, biconvex film-coated tablet, 3.7 mm in diameter, marked with "S" on one side and plain on the other side. Each tablet contains 5 mg of pitolisant hydrochloride equivalent to 4.45 mg of pitolisant.
- Pitolisant 17.8 mg tablets: white, round, plain, biconvex film-coated tablet, 7.5 mm in diameter. Each tablet contains 20 mg of pitolisant hydrochloride equivalent to 17.8 mg of pitolisant.
- Pitolisant 17.8 mg tablets: white, round, biconvex film-coated tablet, 7.5 mm in diameter, marked with "H" on one side and plain on the other side. Each tablet contains 20 mg of pitolisant hydrochloride equivalent to 17.8 mg of pitolisant.

5.1.2. Placebo (Comparator)

Placebo tablets will be provided that match the exact individual physical attributes (as described in Section 5.1.1) for each strength of active pitolisant film-coated tablets (4.45 mg and 17.8 mg).

5.2. Manufacturing, Packaging, and Labeling

Study drug will be manufactured according to current Good Manufacturing Practices.

Study drug will be packaged and labeled by the Sponsor or designee and will be packed and dispatched to comply with controlled shipping and storage conditions. Study drug labeling will comply with all applicable national and local laws and regulations.

5.2.1. Study Drug Packaging and Labeling for the Double-Blind Treatment Phase

Study drug for the Double-Blind Treatment Phase will be packaged as individual patient-specific kits assigned by IRT. Each kit will consist of three boxes, one box for the Titration Period (titration sub-kit) and two boxes for the Stable Dose Period (stable dosing sub-kits; one box containing supplies for Days 22 to 49 and a second box containing supplies for Days 50 to 77).

For individual patients, the number of bottles and contents of the bottles will be based on the patient's randomized treatment assignment and age (Table 7).

The kit for the Double-Blind Treatment Phase for ADULTS will contain:

- Titration sub-kit:
  - Two 10-count bottles, one labeled "A" and one labeled "B" for Week 1 (Days 1 to 7), containing pitolisant 4.45 mg or matching placebo tablets
  - Two 20-count bottles, one labeled "A" and one labeled "B" for Week 2 (Days 8 to 14), containing pitolisant 4.45 mg or matching placebo tablets
  - Two 10-count bottles, one labeled "A" and one labeled "B" for Week 3 (Days 15 to 21), containing pitolisant 17.8 mg or matching placebo tablets
- Stable dosing sub-kits:
  - Two 30-count bottles, one labeled "A" and one labeled "B" for Weeks 4 to 7 (Days 22 to 49), containing pitolisant 17.8 mg or matching placebo tablets
  - Two 30-count bottles, one labeled "A" and one labeled "B" for Weeks 8 to 11 (Days 50 to 77), containing pitolisant 17.8 mg or matching placebo tablets

The kit for the Double-Blind Treatment Phase for ADOLESCENTS will contain:

- Titration sub-kit:
  - Two 10-count bottles, one labeled "A" and one labeled "B" for Week 1 (Days 1 to 7), containing pitolisant 4.45 mg or matching placebo tablets
  - Two 20-count bottles, one labeled "A," one labeled "B," for Week 2 (Days 8 to 14), containing pitolisant 4.45 mg or matching placebo tablets
  - Two 20-count bottles, one labeled "A," one labeled "B," and two 10-count bottles, one labeled "C," and one labeled "D" for Week 3 (Days 15 to 21), containing pitolisant 4.45 mg or matching placebo tablets
- Stable dosing sub-kits:
  - Six 30-count bottles, two labeled "A," two labeled "B," one labeled "C," and one labeled "D" for Weeks 4 to 7 (Days 22 to 49), containing pitolisant 4.45 mg or matching placebo tablets
  - Six 30-count bottles, two labeled "A," two labeled "B," one labeled "C," and one labeled "D" for Weeks 8 to 11 (Days 50 to 77), containing pitolisant 4.45 mg or matching placebo tablets

The kit for the Double-Blind Treatment Phase for CHILDREN will contain:

- Titration sub-kit:
  - One 10-count bottle, labeled "A" for Week 1 (Days 1 to 7), containing pitolisant 4.45 mg or matching placebo tablets
  - One 20-count bottle, labeled "A" for Week 2 (Days 8 to 14), containing pitolisant 4.45 mg or matching placebo tablets

  - Two 20-count bottles, one labeled "A" and one labeled "B" for Week 3 (Days 15 to 21), containing pitolisant 4.45 mg or matching placebo tablets

- Stable dosing sub-kits:
  - Four 30-count bottles, two labeled "A" and two labeled "B" for Weeks 4 to 7 (Days 22 to 49), containing pitolisant 4.45 mg or matching placebo tablets
  - Four 30-count bottles, two labeled "A" and two labeled "B" for Weeks 8 to 11 (Days 50 to 77), containing pitolisant 4.45 mg or matching placebo tablets

5.2.2. Study Drug Packaging and Labeling for the Open-Label Extension Phase

Study drug dosing in the OLE Phase will be as described in Table 8 (prior to implementation of Amendment 6) or Table 9 (following implementation of Amendment 6). Study drug for the OLE Phase will be provided to patients as individual bottles.

Open-label pitolisant for Day 78 through the end of treatment will be provided as 30-count bottles containing pitolisant 4.45 mg or 17.8 mg tablets.

5.3. Storage

At the study site, the Investigator is responsible for ensuring that study drug is stored in a secure location. Responsibilities may be delegated to the pharmacy or other appropriate members of the study team. Responsibilities that are delegated must be documented.

Study drug should be stored at a temperature of 20° to 25° C (68° to 77° F); excursions are permitted between 15° to 30° C (59° to 86° F), in accordance with United States Pharmacopeia (USP) Controlled Room Temperature.

Temperature logs for monitoring proper storage conditions must be maintained by the site.

5.4. Study Drug Administration

Study drug administration for the Double-Blind Treatment Phase and OLE Phase is described in Section 5.4.1 and Section 5.4.2, respectively; additional information for study drug administration will be provided in a separate instructional document.

5.4.1. Study Drug Administration During the Double-Blind Treatment Phase

During the Double-Blind Treatment Phase, patients will take study drug (pitolisant or placebo) once daily in the morning upon wakening in accordance with their randomized dose, as detailed in Table 7. Patients will be instructed to record daily the number of tablets administered from each bottle in the study drug dosing section of the study diary (with the assistance of their caregiver if needed); the time of study drug dosing will be recorded on the day of Visits 3 and 5 and on the day before Visit 4.

5.4.2. Study Drug Administration During the Open-Label Extension Phase

During the OLE Phase, patients will take open-label pitolisant once daily in the morning upon wakening as detailed in Table 8 (prior to implementation of Amendment 6) or Table 9 (after implementation of Amendment 6).

5.5. Study Drug Compliance

Patients/caregivers will be instructed to return all used and unused bottles of study drug at each on-site study visit.

Study drug compliance during the Double-Blind Treatment Phase of the study will be monitored by reviewing the patient study diary in conjunction with the Investigator or designee conducting tablet counts based on the returned study drug. The patient's study diary will be reconciled with tablet counts, and any discrepancies investigated and documented. During TCs, compliance will be monitored by confirming the patient's adherence to study drug administration.

Study drug compliance during the OLE Phase will be monitored during on-site study visits by conducting tablet counts based on the returned study drug. During the OLE TCs, compliance will be monitored by confirming the patient's current dose of study drug and adherence to dosing, as well as shipment/receipt of study drug.

5.6. Study Drug Accountability

The study drug provided for this study will be used only as directed in the study protocol. In accordance with current Good Clinical Practice (cGCP) (International Council for Harmonisation [ICH]-GCP E6 guidelines), Investigators are required to maintain accurate and current records of all study drug to allow reconciliation. The Investigator or designee will acknowledge receipt of study drug, documenting the date received, number and units received, lot numbers, and condition. The Investigator or designee must maintain adequate records of all study drug dispensed, used, returned, and/or destroyed (i.e., accountability or dispensing logs). Sites may destroy drug on site per their own standard operating procedures (SOPs) or study drug may be returned to the Sponsor or designee if necessary.

All study drug records must be readily available for inspection by the site's clinical monitor and/or auditor. No study drug can be returned to the Sponsor or designee or disposed of at the study site until the clinical monitor has reconciled study drug and applicable records at the study site.

5.7. Prior and Concomitant Therapy

Prior medications in the patient's medical record and prior and concomitant medications reported by the patient/parent(s)/legal guardian(s) will be collected. Concomitant medications include prescription and over-the-counter medications (including herbal products and vitamins).

All medications taken by patients between signing of informed consent/assent and the second Safety Follow-up Call (30 days after final dose of study drug, Section 7.5) will be recorded, including dose, regimen, reason for administration, and start date. Changes in concomitant medication will be recorded in the eCRF. Nonpharmacologic therapies/procedures and changes in therapies/procedures will also be recorded in the eCRF. Any prior or concomitant medication used to treat seizure disorders should be recorded in the eCRF.

For patients entering the study on a stable dose of an allowed medication (Section 5.7.1), changes in dosing during the Double-Blind Treatment Phase are not permitted unless medically necessary; if a change in dose is required, the change should be recorded in the eCRF. Any prior or concomitant medication used to treat seizure disorders should be recorded in the eCRF.

5.7.1. Permitted Concomitant Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator and in keeping with the standard of medical care.

With the exception of the prohibited medications specified in Section 5.7.2, patients will be allowed to continue medication(s) for the treatment of PWS or other comorbidities as currently prescribed by their physicians. Patients who are chronically administered sedating medications for management of behavioral manifestations (e.g., hypnotics, benzodiazepines, antipsychotics, alpha agonists, anticholinergics, and antidepressants) must be on stable doses for at least 4 weeks prior to enrollment and remain stable during the Double-Blind Treatment Phase of the study.

The use of diazoxide choline, carbetocin, and oxytocin are permitted if on a stable dose for at least 28 days. Short term use (up to 7 days) of systemic corticosteroids or glucocorticoid use is allowed in consultation with the Medical Monitor.

For concomitant medications administered due to an AE/serious AE (SAE), the Investigator or designee will indicate in the AE/SAE eCRF the concomitant medication administered for the event.

5.7.2. Prohibited 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 are allowed during the OLE Phase of the study, but adjustment of the dose of pitolisant is required (Section 5.7.3).

Pitolisant increases the levels of histamine in the brain; therefore, centrally acting 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 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.

Examples of centrally acting H_1 receptor antagonists, strong CYP2D6 inhibitors, strong CYP3A4 inducers, and medications that may prolong the QT interval are provided in Appendix C.

The investigator should consult with the Medical Monitor for any questions regarding use of prohibited medications during the study.

5.7.3. Medications Requiring Adjustment to the Dose of Pitolisant

Use of strong CYP2D6 inhibitors or strong CYP3A4 inducers is allowed during the OLE Phase; however, if used, the following adjustments to the dose of pitolisant apply:

- Strong CYP2D6 inhibitors: Systemic exposure of pitolisant is increased 2.2-fold in the presence of strong CYP2D6 inhibitors. If initiating treatment with a strong CYP2D6 inhibitor during the OLE Phase, pitolisant dose should be reduced by half.
- Strong CYP3A4 inducers: Systemic exposure of pitolisant is reduced by 50% in the presence of strong CYP3A4 inducers. If initiating treatment with a strong CYP3A4 inducer during the OLE Phase, clinical symptoms should be monitored, and pitolisant dose may need to be increased. Pitolisant dose may only be increased up to the maximum permitted dose based on the patient's age (prior to implementation of Amendment 6; Table 8) [redacted] (following implementation of Amendment 6; Table 9).

Procedures for pitolisant dose adjustments are provided in Section 3.1.5.2.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. Additional information about the timing of assessments is provided in Section 7 and in the Schedule of Assessments for the Double-Blind Treatment Phase and the Schedule of Assessments for the OLE Phase.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history (including any history of seizure disorder and hospitalizations) will be obtained at Screening to ensure patients qualify for the study and will be updated at the Baseline Visit if needed and as necessary thereafter. Confirmation of a patient's diagnosis of PWS will be obtained via review of the patient's medical records; genetic testing will be performed during Screening for patients who do not have documented genetic testing results confirming diagnosis of PWS.

6.1.2. Demographics

Demographic information collected will include date of birth, sex, race, ethnicity, weight, and body mass index (BMI).

6.2. Dosing and Sleep Diary

Patients will be provided with a study diary at the Screening Visit, which will include a study drug dosing section and a sleep diary section.

Patients will be instructed to record in their sleep diary (with the assistance of their caregiver if needed) the time they go to bed each evening and the time they wake up each morning for 14 consecutive nights during the Screening Period, and to return the diary to the study site at the Baseline Visit. Using the patient-recorded times from the sleep diary (at least 7 nights must be recorded for evaluation), a qualified study team member will calculate the evaluable hours and minutes the patient slept per night; patients must have a minimum of 7 evaluable nights from the 14 nights of sleep diary data. Using all evaluable nights, the mean sTST per night for a patient must be at least 8 hours of sleep per night for patients ages 6 to <12 years, at least 7 hours for patients ages 12 to <18 years, or at least 6 hours for patients ages ≥18 years to be eligible to enroll in the study.

Patients will record the number of tablets taken daily from each bottle, starting on the first day of study drug dosing (Day 1) throughout the Double-Blind Treatment Phase. Patients will bring the study drug diary to the site at each visit for review.

An example of the study diary, which includes a sleep diary section and a study drug dosing section, is provided in Appendix B.

6.3. Efficacy Assessments

Patients will be assessed for efficacy using known scales, assessments, and questionnaires. Various symptoms of PWS will be evaluated, including EDS, caregiver and clinician global impressions of severity (for EDS and overall clinical status related to PWS, respectively),

behavior, cognition, and hyperphagia. In addition, the effect of treatment with pitolisant compared with placebo on the perceived caregiver burden with these patients will be evaluated.

In addition, the MERS-R-PWS, which is a modified version of a known scale (the MERS-R) that has been adapted for use in patients with PWS, will be used to assess rigidity in behavior.

6.3.1. Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD); Parent/Caregiver Version

The parent/caregiver version of the ESS-CHAD is an 8-item, 4-point 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: sitting and reading; sitting and watching TV or a video; sitting in a classroom at school during the morning; sitting and riding in a car or bus for approximately half an hour; lying down to rest or nap in the afternoon; sitting and talking to someone; sitting quietly by himself/herself after lunch; sitting and eating a meal. 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 0 = 'would never fall asleep', 1 = 'slight chance of falling asleep', 2 = 'moderate chance of falling asleep', and 3 = 'high chance of falling asleep'. A global score, which represents the sum of responses across all eight items, ranges from 0 to 24; higher scores correspond to greater daytime sleepiness. This assessment will be administered at every on-site study visit. The ESS-CHAD (parent/caregiver version) is provided in Appendix D.

6.3.2. Caregiver Global Impression of Severity for Excessive Daytime Sleepiness

The CaGI-S for EDS is a one-item, 5-point Likert rating scale completed by the patient's parent/caregiver to rate their overall impression of the patient's EDS. At Baseline and at each on-site study visit, caregivers will be asked to rate their impression of the overall severity of the patient's symptoms of EDS over the past week, based on the impact these symptoms have on the patient's ability to function during the day. The CaGI-S for EDS asks the caregiver to rate the patient's likelihood of falling asleep during daytime activities over the past week. The responses for the caregiver completed scale range from 0 = 'not at all" to 4 = "very high likelihood". The CaGI-S for EDS is provided in Appendix E.

6.3.3. Clinical Global Impression of Severity of Overall Clinical Status Related to PWS

The CGI-S is a one-item, 4-point Likert-type rating scale and is a widely used assessment in clinical psychopharmacology trials to assess severity of illness. At Baseline and at each on-site study visit, the Investigator will rate his/her impression of the severity of the patient's current overall clinical status related to PWS relative to the Investigator's experience with this patient population, based on observed and reported symptoms, behavior, and function. The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, please rate the patient's condition at this time". The responses for this investigator-completed scale range from 1 = 'normal' to 4 = 'among the most severely symptomatic' (Busner 2007). The CGI-S is provided in Appendix F.

6.3.4. Aberrant Behavior Checklist-Community, Second Edition

The ABC-C 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 (irritability, social withdrawal, stereotypic behavior, hyperactive/noncompliance, and inappropriate speech). The ABC-C will be completed by the patient's caregiver who will score the items on a 4-point Likert scale ranging from 'not at all a problem' to 'the problem is severe in degree'. The ABC-C is provided in Appendix G.

6.3.5. Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS (MERS-R-PWS)

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

- **Behavioral Rigidity Domain**: difficulty adjusting/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/activities, 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, four items are rated on a scale of 0 to 4, the scores for each domain are added, and the total sum of all three domains is calculated. A higher score reflects more rigid behavior. The MERS-R-PWS is provided in Appendix H.

6.3.6. Cogstate Computerized Cognitive Tests

Cognition will be assessed using the Cogstate Computerized Cognitive Test Battery, a standardized, fully automated, modular battery of tests designed specifically for repeated assessment with minimal practice effects (Collie et al 2003; Falleti et al 2006). The test battery has a short administration time, contains multiple alternate forms, and yields data appropriate for detecting cognitive change. In this study, the cognitive domains of psychomotor function, attention, and working memory will be assessed using the Detection, Identification, and One Back tests, respectively. A pediatric battery will be used for patients 6 to <10 years and an adult battery will be used for patients 10 years and older. Patients will complete two short training sessions to become familiar with the test and to ensure they understand the instructions/task demands.

6.3.6.1. Cogstate Detection Test (Psychomotor Function)

The Cogstate Detection Test is a computerized measure of psychomotor function and uses a validated simple reaction time paradigm with playing card-like stimuli displayed on a computer

screen. In this test, the playing cards all depict the same image. The patient is asked to press the "yes" key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response. The main outcome measure for the test is speed of performance (mean of the log10-transformed reaction times for correct responses). Decreasing scores represent improved test performance.

6.3.6.2. Cogstate Identification Test (Attention)

The Cogstate Identification Test is a computerized measure of visual attention and uses a validated choice reaction time paradigm with playing card-like stimuli displayed on a computer screen. In this test, the playing cards are all either red or black. The patient is asked whether the card displayed in the center of the screen is red. The patient responds by pressing the "yes" key when the card is red and "no" when it is black. The software measures the speed and accuracy of each response. The main outcome measure for the test is speed of performance (mean of the log10-transformed reaction times for correct responses). Decreasing scores represent improved test performance.

6.3.6.3. Cogstate One Back Test (Working Memory)

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 computer screen. The patient is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The patient responds by pressing the "yes" or "no" key. The software measures the speed and accuracy of each response.

6.3.7. 22-Item Zarit Burden Interview

The ZBI-22 (Zarit and Zarit 1990) is a self-reported questionnaire in which caregivers are asked to rate their experience on a 5-point Likert scale (0 = 'never' and 4 = 'nearly always') 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 used to derive the ZBI total score, where higher scores represent greater burden. The ZBI-22 is provided in Appendix I.

6.3.8. Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

The HQ-CT is a 9-item 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 maximum possible score is 36 and scores of approximately 11 to 13 are considered indicative of moderate hyperphagia that may be amenable to treatment. The HQ-CT is provided in Appendix J. The HQ-CT is used in conjunction with the FSZQ, which assesses the level of food environmental control required for patients (Section 6.3.9).

6.3.9. Food Safe Zone Questionnaire (FSZQ)

The FSZQ is a 20-item observer-reported measure of environmental controls that are in place to manage hyperphagia in patients with PWS. The FSZQ will be performed in conjunction with the

HQ-CT (Section 6.3.8). The measure includes four factors: supervision, restricting, avoiding, and checking. 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. The FSZQ questionnaire is provided in Appendix K.

6.3.10. Ghrelin Levels

Serum ghrelin levels (acylated and unacylated) will be assessed during the study as outlined in Section 7.3. Blood samples for ghrelin testing must be performed while the patient is fasting and may be collected at the same time as sample collection for clinical laboratory tests (Table 11).

6.4. Pharmacokinetic Assessments

Pharmacokinetic parameters will include C_{max}, t_{max}, and AUC_{last} of pitolisant and its major metabolite, BP1.3484.

Blood samples for PK evaluations will be collected during the Stable Dose Period of the Double-Blind Treatment Phase (Visits 3, 4, and 5), as detailed in Section 7.3. Consistent with the National Institutes of Health (NIH) Pediatric Blood Volume for Research Guidelines (Howie 2011), the total volume of blood collected is not to exceed the maximal allowable amount of 3.0 mL/kg per day (Appendix A). The estimated total volume of blood to be drawn on PK sampling days, including samples for PK analyses (4.0 mL per sample), serum chemistry tests (5.0 mL per sample), and hematology tests (4.0 mL per sample) is presented in Table 10.

The concentration-time data from this study may be combined with data from previous studies that utilized the same bioanalytical method, and population PK analysis may be conducted. If a population PK analysis is performed, results will be reported separately.

Detailed instructions on PK sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

Table 10: Estimated Total Blood Draw Volumes on Pharmacokinetic Sampling Days

Visit	Blood Sample Volume (mL)			
	PK	Serum Chemistry	Hematology	Total
Visit 3 (Day 22 ±3 days)	4	5	4	13
Visit 4 (Day 50 ±3 days)	20[a]	5	4	29[b]
Visit 5 (Day 76 to 77 ±3 days)	4	5	4	13

PK = pharmacokinetics

[a] Five blood samples (4.0 mL per sample) are to be collected for PK analyses at Visit 4.

[b] Blood draw volume is within the maximum allowable for patients weighing ≥15 kg (Appendix A).

Note: Serum chemistry and hematology parameters are listed in Table 11.

6.5. Safety Assessments

6.5.1. Adverse Events

All AEs, regardless of causality or seriousness, will be collected from the time the patient/parent(s)/legal guardian(s) provides written informed consent/assent through 30 days after final dose of study drug (Safety Follow-up TCs, Section 7.5). Adverse event recording at the Safety Follow-up TCs will include inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]). Additional safety information, including the definition of an AE/SAE and reporting requirements, is provided in Section 8.

Clinically significant findings for laboratory test results, vital signs, ECGs, and abnormal physical examination findings should be recorded as AEs; a clinical diagnosis, rather than the changes in laboratory analyte or other assessment should be recorded.

6.5.2. Physical Examinations

Full or abbreviated physical examinations will be performed at study visits as detailed in Section 7. Full physical examinations will include an evaluation of the head and neck as well as cardiovascular, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems. Abbreviated physical examinations will be performed based on patient/caregiver-reported symptoms.

Height and weight will be measured using standardized methods and recorded on a standardized growth chart per Centers for Disease Control and Prevention (CDC) recommendations (CDC Clinical Growth Charts). Height will be recorded at Screening and at the EOT/ET Visit during the Double-Blind Treatment Phase and at every on-site visit during the OLE Phase. Body weight will be recorded at every on-site study visit.

6.5.3. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be measured at on-site study visits as detailed in Section 7. Patients should be resting for at least 5 minutes before measuring vital signs.

Vital sign measurements will be performed before blood samples are collected for clinical laboratory testing.

6.5.4. 12-Lead Electrocardiograms

12-lead ECGs will be obtained in triplicate for all patients at every on-site study visit as detailed in Section 7. Patients should be resting for at least 5 minutes before the first ECG is performed. All pediatric 12-lead ECGs will be read by a pediatric cardiologist.

ECG testing is to be performed before blood samples are collected for clinical laboratory testing.

Electrocardiogram findings that require discontinuation from the study are specified in Section 4.4.1.

In the Double-Blind Treatment Phase, clinically significant ECG findings (other than those requiring discontinuation from treatment) will require evaluation by the Investigator in consultation with the Medical Monitor.

In the OLE Phase and as noted in Section 4.4.2, any ECG reading that demonstrates QT prolongation should be promptly addressed by the Investigator. 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. At the discretion of the Investigator and in consultation with the Medical Monitor, pitolisant dosing may be temporarily stopped (interrupted) for 2 to 3 days based on clinically significant ECG findings. During an interruption, 12-lead ECGs will be performed daily. Upon resolution of the ECG abnormality, pitolisant administration may resume at the same dose as before the interruption, or the pitolisant dose may be lowered by 50%. If the condition persists after the interruption in dosing, the Investigator, in consultation with the Medical Monitor, will decide whether treatment should be permanently discontinued.

6.5.5. Clinical Laboratory Tests

Clinical laboratory tests will include serum chemistry, hematology, urinalysis, pregnancy tests (serum and/or urine), and urine drug screens as detailed in Table 11. Samples for clinical laboratory tests (serum chemistry and hematology) will be collected as outlined in Section 7.

Consistent with the NIH Pediatric Blood Volume for Research Guidelines (Howie 2011), the total volume of blood collected is not to exceed the maximal allowable amount of 3.0 mL/kg per day (Appendix A). The approximate amount of blood to be collected for clinical laboratory tests at each visit is 9.0 mL (5.0 mL for serum chemistry tests and 4.0 mL for hematology tests).

The Laboratory Manual provides detailed instructions on sample collection, processing, and shipping procedures.

Laboratory test results will be reviewed by the Investigator. Any laboratory value outside of the normal reference range will be evaluated for clinical significance and, if deemed clinically significant, should be reported as an AE with an appropriate diagnosis.

Table 11: 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[a] **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[a,b] **Hematology (4.0 mL blood sample)** -Complete blood count, including platelet count and WBC count with differential -Hemoglobin -Hematocrit -HbA1c

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

[a] Required to be 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.

6.5.6. Additional Safety Assessments

Suicide Risk/Suicidality

Suicide risk at Screening will be assessed through the use of the Very Young Child/Cognitively Impaired–Lifetime Recent C-SSRS (Appendix L). After Screening, suicidality will be evaluated at study visits and TCs through use of the Very Young Child/Cognitively Impaired-Since Last Contact C-SSRS (Appendix M). Any patient with active suicidal behavior or suicidal ideation will be excluded/withdrawn from the study (Section 4.1.2 and Section 4.4.1).

Seizure Disorder

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

Anxiety

The worsening of anxiety or new onset anxiety will be recorded as an AE. In addition, the ADAMS, a 28-item informant-rated scale designed to assess mood and anxiety symptoms will be administered (Esbensen et al 2003). The ADAMS questionnaire is provided in Appendix N.

6.6. Potential Use of Alternative Methods for Completing Study Assessments

To allow for greater flexibility and potentially decrease patient burden related to travel to the study site, specific study assessments may be completed by alternative methods (Table 12 and Table 13).

6.6.1. Assessments that may be Completed Remotely

Specific safety assessments including the assessment of AEs, administration of the C-SSRS and ADAMS, and the review of concomitant medications may be completed by the Investigator and/or site staff remotely using telemedicine technology.

Specific efficacy assessments including administration of the ESS-CHAD (parent/caregiver version), CaGI-S (EDS), CGI-S (overall clinical status related to PWS), ABC-C, MERS-R-PWS, ZBI-22, HQ-CT, and FSZQ may be completed by the Investigator and/or site staff remotely using telemedicine technology.

Other procedures including completing the informed consent process and study drug compliance/accountability review may be completed by the Investigator and/or site staff remotely using telemedicine technology. For patients utilizing the remote visit option, an on-site visit is required once a year. Remote visits cannot be consecutive.

6.6.1.1. Remote Screening Visit

The following assessments for the Screening Visit may be completed remotely by the Investigator or designee using telemedicine technology:

- Informed consent
- Assess/confirm eligibility
- Demographics
- Medical history
- C-SSRS
- ADAMS
- Dispense study diary

- Adverse events
- Concomitant medications
- ESS-CHAD (parent/caregiver version)

The remaining Screening Visit procedures and assessments may be combined with and performed during the Baseline Visit (Visit 2):

- Pregnancy test
- Urine drug screen
- Physical examination
- Body weight
- Height
- Vital signs
- 12-lead ECG
- Clinical laboratory tests
- Genetic testing

Table 12: Remote Screening Visit Combined with On-Site Baseline Visit

Assessment/Procedure	Performed via Telemedicine Screening Visit	Performed at On-Site Baseline Visit
Informed Consent	X	
Assess/confirm eligibility	X	X
Demographics	X	
Medical history	X	X
Urine drug screen		X
Physical examination		X
Body weight		X
Height		X
Vital signs		X
12-lead ECG (in triplicate)		X
C-SSRS	X	X
ADAMS	X	X
Clinical laboratory tests		X
Ghrelin measurements (fasting)		X
Genetic testing		X

Assessment/Procedure	Performed via Telemedicine Screening Visit	Performed at On-Site Baseline Visit
Dispense study diary	X	
Adverse events	X	X
Concomitant medications	X	X
Dispense study drug		X
Administer/titrate study drug		X
ESS-CHAD (parent/caregiver version)	X	X
CaGI-S (of EDS)		X
CGI-S (overall clinical status related to PWS)		X
ABC-C		X
MERS-R-PWS		X
Cogstate Detection[a]		X
Cogstate Identification[a]		X
Cogstate One Back[a]		X
ZBI-22		X
HQ-CT		X
FSZQ		X

ABC-C = Aberrant Behavior Checklist-Community, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CaGI-S = Caregiver Global Impression of Severity; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDS = excessive daytime sleepiness; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; FCBP = female of child-bearing potential; FSZQ = Food Safe Zone Questionnaire; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-R-PWS = Montefiore-Einstein Rigidity Scale – Revised for Research Studies in PWS; PK = pharmacokinetic(s); ZBI-22 = 22-item Zarit Burden Interview

[a] The Cogstate battery practice test is to be administered prior to the actual test.

6.6.1.2. Assessments that may be Completed at the Patient's Home for Visit 3 and/or Visit 4 and for Remote Visits During the Open-Label Extension Phase

The following assessments may be completed by a home healthcare professional at the patient's home under the guidance and supervision of the Investigator:

- Weight
- Height
- Vital signs
- Physical examination
- 12-lead ECG (in triplicate)

- Laboratory assessments
- Other assessments including the Visit 3 PK sampling and study drug accountability

Visit 4 PK samples may be collected at the next on-site study visit, at an unscheduled visit, or at Visit 5 if not able to be collected earlier.

6.6.2. Other Considerations

The Cogstate tests cannot be completed remotely and are required to be completed at the site.

- Visit 4 includes conducting the Cogstate battery of tests. If this visit is not performed as an on-site study visit, the Cogstate testing may either be omitted or completed at a future unscheduled visit prior to Visit 5, should one occur.
- The Cogstate tests to be completed at the EOT visit (Visit 5) are required to be completed at the site. Every effort should be made for Visit 5/EOT to be completed at the study site according to the study schedule.
- Visits 7 and 9 include conducting the Cogstate battery of tests. If either of these visits are completed remotely, the Cogstate testing should be completed at the next on-site visit.

If patients do not attend an on-site study visit, study drug may be sent to patients per the study site's SOPs.

Table 13: Alternative Methods for Completing Study Assessments for Visit 3 and/or Visit 4 and Remote Visits During the OLE Phase

Assessment Scheduled to be Performed at an On-Site Study Visit	Telemedicine	Performed by a Home Healthcare Professional	Potential to be Conducted at the Next On-Site Study Visit or at an Unscheduled Visit
Pregnancy Test (FCBP)		X	
Urine Drug Screen		X	
Physical Examination		X	
Body Weight		X	
Height		X	
Vital Signs		X	
12-Lead ECG (in triplicate)		X	
C-SSRS, ADAMS, ESS-CHAD (parent/caregiver version), CaGI-S, CGI-S, ABC-C, MERS-R-PWS, ZBI-22, HQ-CT, FSZQ	X		
Cogstate Detection, Identification, One Back			X[a]
Clinical Laboratory Tests		X	
Blood Sample for PK		X[b]	X[c]

Assessment Scheduled to be Performed at an On-Site Study Visit	Telemedicine	Performed by a Home Healthcare Professional	Potential to be Conducted at the Next On-Site Study Visit or at an Unscheduled Visit
Adverse Events	X	X	
Concomitant Medications	X	X	
Dispense Study Drug	X		
Study Drug Compliance	X		
Study Drug Accountability	X	X	

ABC-C = Aberrant Behavior Checklist-Community, Second Edition; ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CaGI-S = Caregiver Global Impression of Severity; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDS = excessive daytime sleepiness; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents; FCBP = female of child-bearing potential; FSZQ = Food Safe Zone Questionnaire; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; MERS-R-PWS = Montefiore-Einstein Rigidity Scale –Revised for Research Studies in PWS; PK = pharmacokinetic(s); ZBI-22 = 22-item Zarit Burden Interview

[a] For Visit 4, in the event an unscheduled visit occurs prior to Visit 5/EOT. For Visit 7 and Visit 9, Cogstate tests should be performed at the next on-site study visit.

[b] The Visit 3 PK sample may be collected by the home healthcare professional at the time of collection of other laboratory samples.

[c] Visit 4 PK samples may be collected at the next on-site study visit, an unscheduled visit, or at Visit 5 if not able to be collected earlier.

7. TIMING OF PROCEDURES AND ASSESSMENTS

Information on study procedures and assessments is provided in Section 6. The timing for all assessments is provided in the Schedule of Assessments for the Double-Blind Treatment Phase and the Schedule of Assessments for the Open-Label Extension Phase.

7.1. Screening (Visit 1)

After providing written informed consent/assent, patients will complete screening assessments to assess eligibility to participate in the study. Only patients who meet all eligibility criteria will be enrolled. The Screening Period will be for a maximum of 45 days. Specific procedures and assessments for the Screening visit may be conducted remotely as detailed in Section 6.6.1.

The following evaluations will be performed during the Screening Visit (Visit 1), within 45 days prior to randomization and the first dose of study drug:

- Inclusion/exclusion criteria (Section 4.1)
- Demographics
- Medical history (Section 6.1.1)
- Genetic testing (patients with no documented genetic confirmation of PWS diagnosis)
- Serum pregnancy test (FCBP only)
- Urine drug screen (Table 11)
- Full physical examination (Section 6.5.2)
- Body weight and height (Section 6.5.2)
- Risk of suicide/suicidality (Section 6.5.6 and Appendix L)
- ADAMS (Section 6.5.6)
- Vital signs (Section 6.5.3)
- 12-lead ECGs (in triplicate) (Section 6.5.4)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 11)
- ESS-CHAD (parent/caregiver version)
- Cogstate Detection training
- Cogstate Identification training
- Cogstate One Back training
- AEs (since providing written informed consent/assent)
- Concomitant medications (since providing written informed consent/assent)

Patients will be provided with a study diary that includes a sleep diary section in which they are to record (with the assistance of their caregiver if needed) the time they go to bed each evening and the time they wake up each morning for 14 consecutive nights (at least 7 nights must be recorded for evaluation) (Section 6.2). Patients who do not demonstrate adequate sTST for their

age group (i.e., at least 8 hours of sleep per night for patients ages 6 to <12 years, at least 7 hours for patients ages 12 to <18 years, or at least 6 hours for patients ages ≥18 years), based on their sleep diary, will be considered screen failures. Patients who demonstrate adequate sTST time for their age group, based on their sleep diary, will be randomized via IRT in a 1:1:1 ratio to receive treatment with lower dose pitolisant, higher dose pitolisant, or matching placebo, as detailed in Section 3.1.1.

Patients who fail screening for any reason may be rescreened once at the discretion of the Investigator.

7.2. Baseline (Visit 2; Day -1)

Patients must meet all requirements for inclusion/exclusion criteria, including adequate sTST for their age group based on their sleep diary data (i.e., at least 8 hours of sleep per night for patients ages 6 to <12 years, at least 7 hours for patients ages 12 to <18 years, or at least 6 hours for patients ages ≥18 years; Section 6.2).

The following assessments will also be performed at the Baseline Visit:

- Review of inclusion/exclusion criteria (patients must meet all eligibility criteria)
- Medical history update, as necessary
- Urine pregnancy test (FCBP only)
- Urine drug screen
- Abbreviated physical examination
- Body weight
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)
- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis); may be collected with the fasting serum ghrelin measurement
- Serum ghrelin measurement (fasted; Section 6.3.10; clinical laboratory tests may be collected at the same time as the fasting serum ghrelin measurement)
- Review of AEs
- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)
- ABC-C

- MERS-R-PWS
- Cogstate Detection Test
- Cogstate Identification Test
- Cogstate One Back Test
- ZBI-22
- HQ-CT
- FSZQ

Eligible patients will be dispensed a study drug titration kit at the Baseline Visit (Section 5.2.1) and will be instructed to take study drug once daily in the morning upon wakening. Patients will be instructed to take their first dose of study drug on the day after the Baseline Visit (the first day of study drug dosing is Day 1).

Patients will be instructed to record daily the date and number of tablets of study drug taken from each bottle in the study drug dosing section of the study diary (with the assistance of their caregiver, if needed) (Appendix B).

Patients and their caregivers will be instructed to bring the study diary and all used and unused bottles of study drug with them to all on-site study visits. The study diary will be completed only during the Double-Blind Treatment Phase of the study.

7.3. Double-Blind Treatment Phase (Day 1 to Day 77)

Section 3.1.3 provides details on study drug dosing during the Double-Blind Treatment Phase of the study.

7.3.1. Titration Period, Double-Blind Treatment Phase (Days 1 to 21)

Patients will take their first dose of blinded study drug on the day after the Baseline Visit and will be titrated to their randomized stable dose during a 3-week Titration Period. The first dose of study drug will be Day 1, and study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized stable dose, as described in Table 7); all patients will be at their randomized stable dose of study drug by Day 15.

No on-site study visits are scheduled during the Titration Period in the Double-Blind Treatment Phase. Patients and/or their caregivers will be contacted by the study site by telephone on Days 8 and 15 (±3 days; TCs 1 and 2, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug dose.

7.3.2. Stable Dose Period, Double-Blind Treatment Phase (Days 22 to 77)

Patients will continue to take study drug at their randomized stable dose during the Stable Dose Period and will return with their caregivers to the study site on Day 22, Day 50, and Day 77 (±3 days; Visits 3, 4, and 5, respectively) for safety, efficacy, and PK assessments. Patients and/or their caregivers will be contacted by the study site by telephone on Days 29, 36, and 57 (±3 days; TCs 3, 4, and 5, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS and ADAMS, and confirm compliance with study drug administration.

The last dose of blinded treatment is on Day 77 ±3 days (Visit 5; EOT Visit in the Double-Blind Treatment Phase).

7.3.2.1. Visit 3 (Day 22 ±3 Days)

The patient (with the assistance of their caregiver if necessary) should record in the study diary the time of study drug dosing on the morning of Visit 3. The following evaluations will be performed at Visit 3:

- Urine pregnancy test (FCBP only)
- Abbreviated physical examination
- Body weight
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)
- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Blood sample collection for PK analyses (sample may be collected at the same time as clinical laboratory tests; time of last dose of study drug and time of blood sample collection to be recorded) (Section 6.4).
- Review of AEs
- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)
- ABC-C
- MERS-R-PWS
- ZBI-22
- HQ-CT
- FSZQ
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Patients will be dispensed study drug at this visit.

7.3.2.2. Telephone Calls; TC 3, TC 4, and TC 5 (Days 29, 36, and 57 [±3 Days])

Patients and/or their caregivers will be contacted by the study site by telephone on Days 29, 36, and 57 (±3 days; TCs 3, 4, and 5, respectively) to assess for AEs and use of concomitant

medications, complete the C-SSRS, ADAMS, and confirm compliance with administration of study drug.

7.3.2.3. Visit 4 (Day 50 ±3 Days)

To accommodate PK sample collection at Visit 4, patients will not take their daily dose of study drug before arriving at the study site. Patients and their caregivers will bring study drug and study diary with them to the study visit (time of study drug administration on the day before Visit 4 should be recorded in the study diary).

Study drug administration will be at the study site; the timing of study drug administration will be based on the PK sampling schedule.

Blood Sample Collection for PK:

A blood sample for PK analyses will be collected before administration of study drug at the study site (the time of sample collection is to be recorded).

After the first blood sample for PK analyses is collected, patients will be administered study drug (the time of study drug administration is to be recorded).

Additional blood samples for PK analyses will be collected at the following times after study drug administration (the time of each blood sample collection is to be recorded):

- 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

The following evaluations will also be performed at Visit 4:

- Urine pregnancy test (FCBP only)
- Abbreviated physical examination
- Body weight
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)
- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Review of AEs
- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)

- ABC-C
- MERS-R-PWS
- Cogstate Detection Test
- Cogstate Identification Test
- Cogstate One Back Test
- ZBI-22
- HQ-CT
- FSZQ
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Blood draw volumes at Visit 3 are not to exceed the maximal allowable of 3.0 mL/kg per day (Appendix A and Table 10).

Patients will be dispensed study drug at this visit.

7.3.2.4. Visit 5 (Day 77 ±3 Days); End of Treatment in the Double-Blind Treatment Phase

Visit 5 (Day 77 ±3 days) is the EOT visit in the Double-Blind Treatment Phase of the study. A fasting blood sample for ghrelin testing will be collected at this visit; therefore, the patient should fast on the night before Visit 5. The patient (with the assistance of their caregiver if necessary) should record in the study diary the time of study drug dosing on the morning of Day 77, Visit 5. The following evaluations will be performed at Visit 5:

- Urine pregnancy test (FCBP only)
- Urine drug screen
- Full physical examination
- Body weight and height
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)
- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis); may be collected with the fasting serum ghrelin measurement and the PK blood sample collection
- Serum ghrelin measurement (fasting)
- Blood sample collection for PK analyses (sample may be collected at the same time as clinical laboratory tests and fasting serum ghrelin measurement; time of last dose of study drug and time of blood sample collection for PK is to be recorded)
- Review of AEs

- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)
- ABC-C
- MERS-R-PWS
- Cogstate Detection Test
- Cogstate Identification Test
- Cogstate One Back Test
- ZBI-22
- HQ-CT
- FSZQ
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Patients will be given the opportunity to participate in the OLE Phase at this visit. Eligible patients who enter the optional OLE Phase will be dispensed open-label pitolisant (Section 5.2.2); eligibility criteria must be confirmed before patients receive open-label pitolisant. Patients will be instructed to begin taking open-label pitolisant on the following day in the morning upon wakening (Day 78 ±3 days).

Patients who do not enter the OLE Phase will be receive Safety Follow-up TCs from the study site 15 days (± 3 days) and 30 days (+3 days) after last dose of blinded treatment, as outlined in Section 7.5.

7.3.3. Early Termination Visit for Double-Blind Treatment Phase

Every effort should be made to perform the ET evaluations for patients who terminate early from the Double-Blind Treatment Phase of the study. At the ET Visit, the reason for early termination must be recorded. The safety and efficacy evaluations to be performed at the ET visit are the same as those listed for Visit 5 (Section 7.3.2.4).

Patients who discontinue from the Double-Blind Treatment Phase prior to Day 77 may enroll in the OLE Phase following approval from the Medical Monitor in consultation with the Investigator (eligibility criteria must be confirmed).

7.4. Open-Label Extension Phase (Day 78 To End of Treatment)

Section 3.1.4 provides details on study drug dosing for the OLE Phase of the study. Dose adjustments are permitted in the OLE Phase; pitolisant dose can be adjusted (higher or lower) as outlined in Section 3.1.5.2.

7.4.1. Titration Period; OLE Phase (Days 78 to 98)

Table 8 and Table 9 detail the dosing regimens for the OLE Phase. Patients will receive their first dose of open-label pitolisant on Day 78 (±3 days).

Patients and/or their caregivers will be contacted by the study site by telephone on Days 85 and 92 (±3 days; TCs 6 and 7, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm dosing and administration of study drug.

7.4.2. Long-Term Dosing Period, OLE Phase (Day 99 to End of Treatment)

Patients will continue to take open-label pitolisant at their target dose during the OLE Long-Term Dosing Period as detailed in Table 8 (prior to implementation of Amendment 6) and Table 9 (after implementation of Amendment 6), with dosing adjustments permitted as described in Section 3.1.5.2.

Patients and their caregiver will return to the study site on Day 99 ±3 days (Visit 6) and again on Days 189, 279, and 369 (±7 days) (Visits 7, 8, and 9, respectively) for assessment of safety and effectiveness as detailed in Section 7.4.2.1.

After completion of Visit 9, patients and/or their caregivers will receive a TC from the study site on Day 459 (±7 days; TC 8) and approximately every 6 months (180 ±7 days) thereafter as detailed in Section 7.4.2.2. Patients and their caregivers will return to the study site on Day 549 (±7 days; Visit 10) and approximately every 6 months (180 ±7 days) thereafter as detailed in Section 7.4.2.3. This pattern of alternating TCs and on-site study visits will be repeated until either the patient discontinues from the study or the Sponsor elects to terminate the study.

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; (Section 7.4.2.1); 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 (Section 7.4.2.3). An on-site visit is required once a year. Remote visits cannot be consecutive.

7.4.2.1. Visits 6, 7, 8, and 9 (Days 99, 189, 279, and 369)

Patients will have the option to complete up to two of the scheduled on-site study visits (Visits 6, 7, 8, and 9) remotely; assessments associated with on-site study visits that may be completed remotely are detailed in Section 6.6. Except where specified, patients will complete all of the following assessments at Visits 6, 7, 8, and 9 (the window for Visit 6 is ±3 days and ±7 days for all other visits):

- Urine pregnancy test (FCBP only)
- Full physical examination
- Body weight and height
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)

- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Urine drug screen
- Review of AEs
- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)
- ABC-C
- MERS-R-PWS (Visits 7 and 9 only)
- Cogstate Detection Test (Visits 7 and 9 only)
- Cogstate Identification Test (Visits 7 and 9 only)
- Cogstate One Back Test (Visits 7 and 9 only)
- ZBI-22
- HQ-CT
- FSZQ
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Patients will be dispensed study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily treatment at each visit.

7.4.2.2. Telephone Calls; Day 459 (TC 8) and Every 6 Months (180 Days) Thereafter Until End of Treatment

Patients remaining in the study and receiving study drug after Visit 9 will receive a TC on Day 459 ±7 days (TC 8) and approximately every 6 months (180 days ±7 days) thereafter until either the patient withdraws from the study or the Sponsor elects to terminate the study.

The following will be assessed at TC 8 and each subsequent TC:

- Review AEs
- Review concomitant medications
- C-SSRS
- Confirm study drug dose
- Confirm shipment/receipt of their next 3-month (90-day) supply of study drug

Additionally, if applicable, patients will receive two safety follow-up TCs, one 15 days (±3 days) and one 30 days (+3 days) after taking the final dose of study drug as detailed in Section 7.5.

7.4.2.3. Visit 10 (Day 549) and Every 6 Months (180 Days) Thereafter Until End of Treatment

Patients remaining in the study and receiving study drug after TC 8 will return with their caregivers to the study site on Day 549 ±7 days (Visit 10) and approximately every 6 months (180 days ±7 days) thereafter until either the patient withdraws from the study or the Sponsor elects to terminate the study; these patients may complete one on-site study visit remotely per year (Section 6.6 describes assessments associated with on-site study visits that may be completed remotely).

Patients will be dispensed study drug for 3 months (i.e., 90 days) for once daily administration, which is a quantity sufficient until the next scheduled telephone call.

The following assessments will be performed at Visit 10 and at each subsequent study visit:

- Urine pregnancy test (FCBP only)
- Full physical examination
- Body weight and height
- Vital signs
- 12-lead ECG (in triplicate)
- C-SSRS (Appendix M)
- ADAMS
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- Urine drug screen
- Review of AEs
- Review of concomitant medications
- ESS-CHAD (parent/caregiver version)
- CaGI-S (for EDS)
- CGI-S (for overall clinical status related to PWS)
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Patients will be dispensed study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration at each visit.

7.4.2.4. End of Treatment Visit for the Open-Label Extension Phase

Patients are to complete an EOT Visit after they complete the study; the evaluations of safety and effectiveness to be performed at the EOT Visit in the OLE Phase are the same as those listed for Visit 10 (Section 7.4.2.1).

7.4.3. Early Termination Visit for Open-Label Extension Phase

Every effort should be made to perform the ET evaluations for patients who terminate early from the OLE Phase of the study. At the ET Visit, the reason for early termination must be recorded. The evaluations of safety and effectiveness to be performed at the ET visit are the same as those listed for Visit 10 (Section 7.4.2.1).

7.5. Safety Follow-Up Telephone Calls

Patients in the Double-Blind Treatment Phase who do not enter the optional OLE Phase will receive a TC from the study site 15 days (±3 days) and 30 days (+3 days) after their final dose of study drug 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 use of concomitant medications and to complete the C-SSRS and ADAMs.

Patients (and/or their caregivers) in the OLE Phase will receive a TC from the study site 15 days (±3 days) and 30 days (+3 days) after their final dose of study drug 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 use of concomitant medications and to complete the ADAMS.

An on-site unscheduled study visit will be requested for any patient reporting signs and symptoms of arrhythmia or cardiac manifestations, and/or a psychiatric event at either of the two Safety Follow-up TCs (Section 7.6).

7.6. Unscheduled Visits and Assessments

Unscheduled visits and assessments in the Double-Blind Treatment Phase and OLE Phase of the study 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.

At minimum, the following assessments are to be performed at an unscheduled on-site study visit:

- Abbreviated physical examination
- Body weight
- Height
- Vital signs
- Review of AEs
- Review of concomitant medications
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Other assessments (e.g., 12-lead ECGs, clinical laboratory tests, urine pregnancy test, Very Young Child/Cognitively Impaired-Since Last Contact C-SSRS, ADAMS, ABC-C) can be completed based on the reason for the unscheduled visit and at the Investigator's discretion.

At a minimum, AEs, concomitant medication use, and study drug accountability/compliance should be assessed during unscheduled TCs. Other assessments (e.g., Very Young Child/Cognitively Impaired-Since Last Contact C-SSRS, ADAMS, ABC-C) can be completed based on the reason for the unscheduled TC and at the Investigator's discretion.

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection and documentation of events that meet the definition of an AE, SAE, suspected adverse reaction, serious suspected adverse reaction, or unanticipated problem, as provided in this protocol.

Investigators must review the WAKIX (pitolisant) IB to be knowledgeable about the study drug and aware of its safety profile. Investigators will also be versed in the latest standard of care guidelines.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal physical examination findings, laboratory value, vital sign result, or ECG finding that is deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE. A clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (e.g., anemia rather than low hemoglobin value).

Examples of AEs include:

- Significant or unexpected worsening or exacerbation of the condition or indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding related to the condition).
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur).
- A diagnosis related to any clinically significant abnormal laboratory test result.
- Any laboratory abnormality not associated with a diagnosis or symptom requiring further diagnostic investigation.

The following examples would not be considered AEs:

- Medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure would be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen during the study.

- The disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the patient's condition.

8.1.2. Definition of a Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (i.e., presented an immediate risk of death from the event as it occurred; this criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following events do not meet the definition of an SAE:

- Hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline
- Hospitalization for a standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition
- Social or convenience admission to a hospital
- Prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE
- Hospitalization or an emergency room visit that lasts less than 24 hours that does not meet the criteria of an important medical or a life-threatening event

8.1.3. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the AE was caused by the study drug.

8.1.4. Definition of a Serious Suspected Adverse Reaction

A serious suspected adverse reaction is any suspected adverse reaction that is determined to be serious, based on the definition of an SAE described in Section 8.1.2.

8.1.5. Definition of Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that meet all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the Ethics Committee (EC; includes Institutional Review Boards [IRBs], Independent ECs, and Research Ethics Boards) and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggest that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

The Investigator will assess the severity of each AE based on his/her clinical judgment using one of the following categories:

- **Mild:** Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- **Severe:** Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.2.2. Relationship to Study Drug

The Investigator will assess the relationship (i.e., causality) of each AE to study drug based on his/her clinical judgment. The Investigator's assessment of the relationship of an AE to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study drug assessed. The Sponsor's assessment of relationship may differ from the Investigator's assessment.

Relationship to study drug will be assessed according to the following guidelines:

- **Not related:** There is not a temporal relationship to study medication administration, or the AE is clearly and incontrovertibly due only to progress of the underlying disease or to extraneous causes.
- **Unlikely related:** There is little or no chance that the study treatment caused the reported AE; the event is most likely because of another competing cause, including concomitant illnesses, progression or expression of the disease state, or a reaction to a concomitant medication.
- **Possibly related:** The association of the AE with study treatment is unknown; however, the AE is not reasonably attributed to any other condition.
- **Probably related:** A reasonable temporal association exists between the AE and study treatment, and based on the Investigator's clinical experience, there is no other obvious competing cause. The event responds to withdrawal of the study medication (positive dechallenge) and rechallenge with administration of the study medication is ambiguous or not done.
- **Definitely related:** There is a reasonable causal relationship between study treatment and the AE; the event responds to withdrawal of the study medication (positive dechallenge) and recurs with rechallenge by administration of the study medication.

For initially reporting SAEs, even in situations in which minimal information is available, it is important that for every event the Investigator make an assessment of causality. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality based on follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

8.3. Time Period and Frequency for Adverse Event Assessment and Follow-up

8.3.1. Adverse Event and Serious Adverse Event Monitoring

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, Section 7.5).

For patients who receive study drug in the Double-Blind Phase and do not enter the OLE Phase of the study, if an Investigator becomes aware of an SAE that occurs at any time after the patient's study participation and the Investigator considers the event to be possibly related to the study drug, the Investigator should report the SAE to the Sponsor as described in Section 8.4.1.

8.3.2. Follow-up of Events

After the occurrence of an AE or SAE, the Investigator is required to follow each patient proactively and provide further information on the patient's condition. All AEs and SAEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

All AEs and SAEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or the event is otherwise explained or judged by the Investigator to be no

longer clinically significant (unless the patient is lost to follow-up or the patient/parent(s)/legal guardian(s) withdraws consent).

The Investigator will assess the outcome of each AE using the following categories:

- **Recovered/Resolved:** The event resolved, or the patient recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the patient experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Recovered/Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Recovering/Resolving:** The event is improving.
- **Not recovered/Not resolved:** At the end of the study, an event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The patient is lost to follow-up, and the status of the event is unknown.
- **Death**

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

During this study, if the Investigator determines that an event meets the protocol definition of an SAE, regardless of relationship to study drug, they must notify the Sponsor as soon as possible but no later than **24 hours of becoming aware of the SAE**. The SAE report form (completed with all available information) must be sent to the Sponsor via e-mail or facsimile as soon as possible but no later than **within 24 hours of the Investigator becoming aware of the SAE**. The investigator must be diligent about providing additional information as needed. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

In the initial email, the Investigator must provide to the Sponsor the following eCRF pages, completed to the greatest extent possible:

- AE record
- Medical history
- Prior and concomitant medications

Also, any laboratory test results, diagnostic test results, or medical reports relevant to the SAE should be provided; however, certain patient identifying information (i.e., name, address, and other identifying information not collected in the patient's eCRF) is to be redacted from copies of the patient's medical records.

In rare circumstances and in the absence of email capacity, a copy of the SAE reporting form can be sent to the Sponsor by overnight mail. Initial notification of the event via telephone or email does not replace the need for the Investigator to complete the appropriate SAE form within the time frames outlined and email the form (or in the absence of email/scanning capacity--overnight mail is acceptable in rare cases). In addition, the AE/SAE information for the event needs to be entered in the eCRF.

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the Sponsor using the same 24-hour timelines as for an initial report.

In the event of a medical emergency in which knowledge of the patient's treatment assignment may influence their clinical care, the Investigator has the option to unblind the patient's treatment assignment via the IRT system. The Investigator should make every effort to contact the Medical Monitor prior to unblinding unless this would adversely delay appropriate medical care. The Medical Monitor will not be unblinded and will only provide assistance to the Investigator. The reasons for unblinding must be noted in the source documents. The Investigator must not disclose the patient's treatment assignment to anyone who does not need the information based on their direct involvement in the patient's clinical care. Disposition of patients who are unblinded due to a medical emergency will be determined following discussion with the Sponsor.

In the event of death, every effort should be made to obtain a death certificate and if possible, an autopsy report. Death is considered an outcome of an event; however, if the event that resulted in death is unknown, death will be recorded as the event.

8.4.2. Reporting Unanticipated Problems to the Sponsor

If the Investigator determines that an event meets the protocol definition of an unanticipated problem, he/she must notify the Sponsor **within 24 hours of becoming aware of the problem**.

The following information should be included with unanticipated problem reporting:

- Protocol identifying information: protocol title, protocol number, and Investigator's name
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem

It is the Investigator's responsibility to report unanticipated problems to the Sponsor and the IRB, as required by local regulations.

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that serious suspected adverse

reactions that are either unexpected or observed with increasing occurrence can be reported and legal obligations and ethical responsibilities regarding the safety of other patients are met.

Investigator letters are prepared according to Sponsor policy and are forwarded to Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is both serious and unexpected. The purpose of an Investigator letter is to fulfill specific regulatory and cGCP requirements regarding the product under investigation.

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB.

The Sponsor is responsible for informing IRBs, Investigators, and regulatory authorities of any finding that could adversely affect the safety of patients or affect the conduct of the study. Events will be reported to regulatory authorities in accordance with expedited reporting requirements.

8.4.4. Pregnancy Reporting

Pregnancy is not considered an SAE; however, it is documented and followed in the same manner as an SAE. Any patient who becomes pregnant during the study must be withdrawn from the study immediately. Patients who become pregnant within 30 days after receiving their final dose of study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on the outcome and health status of the mother and child.

The Investigator must notify the Sponsor of any pregnancy by completing a Pregnancy Form and emailing it to the Sponsor **within 24 hours of becoming aware of the pregnancy**.

9. STATISTICAL CONSIDERATIONS

9.1. General Considerations

All safety and efficacy data will be listed and summarized. Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to study drug administration. Safety and efficacy endpoints will be summarized by treatment group and the active treatment groups pooled. Continuous variables will be summarized using the number of patients with data (n), mean, standard deviation (SD), median, minimum, and maximum. Selected continuous variable summaries will also include the standard error. Categorical variables will be summarized using frequency counts and percentages.

The statistical analysis plan (SAP) will provide further details for statistical methodology. If the statistical analyses described in the final SAP and final protocol differ, the statistical analyses in the SAP will be used for the analyses presented in the clinical study report (CSR). Substantive changes from the analyses specified in the protocol will be described in the SAP and in the CSR.

In general, continuous variables will be summarized using the number of non-missing values, mean, SD, median, minimum, and maximum; categorical variables will be summarized using the count and the percentage of patients in each category. All values summarized will also be presented in listings.

All analyses will be performed using SAS® version 9.4 or higher, unless otherwise specified.

9.1.1. Estimand

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

The target population is all patients in the intent-to-treat (ITT) 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 mixed model repeated measures (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.

9.1.2. Multiple Comparisons

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

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.

- Primary endpoint: Change in ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for the higher dose pitolisant group compared with placebo.

- Primary endpoint: Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for the lower dose pitolisant group compared with placebo.
- Primary endpoint: Change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for the combined pitolisant dose groups compared with placebo.
- Secondary endpoint: Change in CaGI-S for EDS from Baseline to Week 11 for the higher dose pitolisant group compared with placebo.
- Secondary endpoint: Change in CGI-S for overall clinical status from Baseline to Week 11 for the higher dose pitolisant group compared with placebo.
- Secondary endpoint: Change in CaGI-S for EDS from Baseline to Week 11 for the lower dose pitolisant group compared with placebo.
- Secondary endpoint: Change in CGI-S for overall clinical status from Baseline to Week 11 for the lower dose pitolisant group compared with placebo.

Likewise, the effect of treatment with pitolisant (higher dose, lower dose, and pooled) compared with placebo on other secondary outcomes will be tested in the order outlined in the SAP. These include the change from Baseline to Week 11 in behavior as measured by ABC-C and MERS-R-PWS; cognition as measured by Cogstate Detection, Identification and One Back tests; and perceived caregiver burden as measured by ZBI-22.

9.1.3. Missing Data

Every effort will be made to retain patients in the study; however, patients are able to withdraw from the study at any time for any reason. Patients who withdraw early will be asked to return to the clinic for an ET visit for completion of assessments (Section 7.3.3 and Section 7.4.3). 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 (MAR).

A sensitivity analysis will be performed using a hypothetical strategy. In this approach, the unobserved data following discontinuation for lack of efficacy (LOE) 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 MAR.

This will be implemented using a three-stage multiple imputation (MI) approach:

1. Intermittent missing data will be imputed within treatment group using MI under a MAR assumption with covariates for site and observed values at all available time points (including baseline). Twenty values will be produced using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, producing a monotone missing data pattern.
2. Patients who drop out for reasons other than LOE or AEs will likewise have their missing values following dropout imputed within treatment group with covariates for site and observed values at all available time points (including baseline).
3. Finally, patients who withdraw from the study due to LOE or AEs will have their missing values following discontinuation imputed using the placebo group distribution, regardless of their assigned treatment group.

9.2. Determination of Sample Size

The sample size is 60 patients (20 in the lower dose pitolisant group, 20 in the higher dose pitolisant group, and 20 in the placebo group). Prior research suggests that the ESS-CHAD SD falls between 5 to 6; at the lower end of this range, the study would be powered at 80% to detect a difference of 3.9 between the pooled pitolisant groups and placebo group. However, as a proof of concept, statistical separation is not a strict objective of the trial. The proposed sample size will yield a 95% confidence interval of ±2.7 with an SD of 5 and ±3.2 with an SD of 6; this will give sufficient precision to inform future studies.

9.3. Analysis Populations

The safety analyses will be conducted on the safety population. The ITT population will be used for the primary 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 treatment received for safety assessments.

9.3.1. Intent-to-Treat Population

The ITT 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. This population will be used to summarize the primary and other efficacy data. Patients will be analyzed according to randomized treatment assignment.

9.3.2. Double-Blind Safety Population

The double-blind safety population will include all patients who are enrolled 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, patients will be counted at the highest dose they received in the Double-Blind Treatment Phase.

9.3.3. Open-Label Safety Population

The open-label safety population will include all patients who are enrolled in the OLE Phase and take at least one dose of open-label study drug.

9.3.4. Pharmacokinetic Population

The PK population will include all patients who received at least one dose of pitolisant and have calculable PK parameters available for analysis.

9.4. Statistical Analysis Methods

9.4.1. Disposition and Demographics

The number and percentage of patients in each analysis population will be summarized. The number of patients screened and patients enrolled and treated and the number and percentage of patients completing the Double-Blind Treatment Phase of the study, discontinuing from the Double-Blind Treatment Phase of the study (including reasons for discontinuation), and entering

the OLE Phase (with and without completion of the double-blind) will be summarized. All percentages will be calculated using the number of patients enrolled as the denominator.

Additionally, for the open-label safety population, the number of patients enrolled in the OLE Phase, the number and percentage of patients completing the OLE Phase of the study, and the number of patients discontinuing from the OLE Phase of the study (including reasons for discontinuation) will be summarized. All percentages will be calculated using the number of patients enrolled in the OLE Phase as the denominator.

Demographics and baseline characteristics will be reported for the efficacy, double-blind safety, and open-label safety populations. Categorical items will be reported with counts and percentages; continuous items will be reported using summary statistics (mean, SD, median, minimum, maximum). 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.

9.4.2. Efficacy Analysis

9.4.2.1. Double-Blind Treatment Phase

9.4.2.1.1. Primary Efficacy Analysis

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint of change in mean ESS-CHAD (parent/caregiver version) score from Baseline to Week 11 for pitolisant compared with placebo will be reported by treatment group and for the active groups combined. The change from Baseline will be analyzed in an MMRM analysis. Fixed effects will be included for treatment, Baseline value, visit, and treatment×visit interaction. An unstructured covariance matrix will be utilized, and if this fails to converge, then first-order autoregressive and compound symmetry will be attempted in that order; Kenward-Rogers degrees of freedom will be used. Least square (LS) means, standard errors, and the LS mean differences (each treatment vs placebo and the pooled active groups vs 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 contrast of interest is the difference in the higher dose group versus placebo at Week 11.

Sensitivity analyses will utilize an approach identical to the primary analysis but on the dataset with imputed values. The 20 repeats will each be modeled independently, then combined using SAS Proc MI analyze and Rubin's approach (Rubin 1976).

9.4.2.1.2. Secondary Efficacy Analysis

Continuous outcomes collected at multiple time points will be analyzed with summary statistics (mean, SD, median, minimum, maximum) for the absolute values and change from baseline at each timepoint by treatment group and for the active groups combined. The change from baseline will be analyzed using an MMRM approach. Fixed effects will be included for treatment, visit, treatment×visit interaction, and Baseline value. An unstructured covariance matrix will be utilized, and if this fails to converge, then first-order autoregressive and compound symmetry will be attempted in that order; Kenward-Rogers degrees of freedom will be used. Least square means, standard errors, and the LS mean differences (each treatment vs placebo and the pooled active groups vs placebo) at each time point 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 contrast of interest is the difference in the higher dose group versus placebo at Week 11.

9.4.2.1.3. Exploratory Efficacy Analysis

The analyses used for the secondary outcomes will be applied to the exploratory outcomes for the full study cohort and repeated within each age group (i.e., change from Baseline to Week 11 in HQ-CT and acylated and unacylated ghrelin levels) as feasible. The MMRM may be replaced with an analysis of covariance (ANCOVA) at Week 11 or a simple t-test if sample size does not permit more complicated modeling approaches within an age group.

9.4.2.2. Open-Label Extension Analyses

Results 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. Details of open-label analyses will be described in the SAP.

9.4.3. Safety Analysis

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.

Adverse events that occur between the time written informed consent/assent is provided and the start of study drug administration will be considered pretreatment AEs. A TEAE is:

- any AE reported after the first dose of study drug and up to 30 days after last dose of study drug, or
- any worsening of a pre-existing condition reported after first dose of study drug and up to 30 days after last dose of study drug.

All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized. Adverse events leading to study withdrawal, if any, will be listed separately.

Laboratory parameters will be summarized over time using descriptive statistics. For each laboratory test, individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline to the lowest and to the highest on study value as well as by visit. Shift tables will include the categories of low, normal, and high as defined by the normal ranges provided by the central laboratory.

The change from Baseline to each visit for vital sign variables will be summarized using descriptive statistics. Abnormal vital sign values will be flagged and listed. Changes from baseline in ECG results (heart rate and PR, RR, QRS, QT, QTcF, and QTcB intervals) will be summarized. Categorical summaries based on QTcF will be provided to show changes from baseline in QTcF >60 msec, and actual values >442 msec for patients ages 0 to <10 years and >439 msec for patients ages 10 to <20 years, regardless of gender, and >450 msec for male patients and >470 msec for female patients ages 20 to 65 years, as well as QTcF >500 msec regardless of age or gender.

Results of C-SSRS and ADAMS will be listed.

9.4.4. Pharmacokinetic Analyses

Concentration-time profiles will be plotted on semi-log and linear scales for each individual patient as spaghetti plots and summarized by treatment group and age.

The following steady-state PK parameters will be determined using noncompartmental methods: C_{max}, AUC_{last}, and t_{max} of pitolisant and its major metabolite, BP1.3484. Pharmacokinetic parameters will be summarized overall and by treatment group and age. The following summary statistics will be considered for concentration-time data: mean, SD, coefficient of variation (CV%), median, minimum, and maximum. These summary statistics will also be conducted for PK parameters (except t_{max}) along with the geometric mean, geometric SD, and geometric CV%. The median, minimum, and maximum will be calculated for t_{max}.

The 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; results will be provided in a separate report.

9.5. Interim Analysis

No interim analyses are planned for this study; 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.

10. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control systems will be implemented and maintained with SOPs by the Sponsor and its designee(s), as appropriate, to ensure that the clinical study is conducted and the data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP E6 guidelines, and applicable regulatory requirements. The accuracy, completeness, and reliability of the study data presented to the Sponsor are the responsibility of the Investigator. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

The study will be monitored regularly by the Sponsor (Section 12.1) and may be audited or inspected by the Sponsor (or designee), IRB, and/or regulatory authorities at any time during the study or after study completion. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory agencies direct access to all study records. The Investigator will immediately notify the Sponsor of all audits or inspections scheduled by any regulatory authority and promptly forward copies of any audit or inspection reports received to the Sponsor.

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the study in that country.

11.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and all applicable regulatory requirements in accordance with ICH/cGCP and in general conformity with the most recent version of the Declaration of Helsinki.

11.3. Institutional Review Board Approval

The Investigator, Sponsor, or designee is responsible for submitting the following documents to the IRBs for review and, if applicable, approval: study protocol, informed consent/assent form(s), IB, recruitment materials, information about study compensation to patients, and any information provided to potential patients.

The Investigator is responsible for providing the Sponsor with the written IRB approval prior to commencing the study (i.e., before shipment of study drug to the site). All amendments to the protocol require review and approval by the IRB before the changes are implemented to the study. All changes to the informed consent/assent form will be approved by the IRB; a determination will be made regarding whether previously consented participants need to be reconsented. If any other information approved by the IRB for presentation to potential patients is amended during the study, the Investigator is also responsible for ensuring IRB review and approval.

Study sites must adhere to all requirements stipulated by their respective IRBs. This may include, but is not limited to, notifying the IRB of serious and unexpected AEs or other information based on local safety reporting requirements, submitting a final status report, or providing a synopsis of the study report upon study completion.

11.4. Informed Consent/Assent Process

All references to "patient" in this section refer to the study patient or his/her parent(s)/legal guardian(s)/legally authorized representative.

The Sponsor (or its designee) will provide Investigators with an informed consent/assent form for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 Code of Federal Regulations [CFR] Part 50.25). The final informed consent/assent form must be accepted by the Sponsor and approved by the IRB/EC. Investigators must provide the Sponsor with an unsigned copy of the final informed consent/assent form before and after it is approved by the IRB/EC. If any new information becomes available that might affect patients' willingness to participate in the study, or if any amendments to the protocol require changes to the informed consent/assent form, the Sponsor will provide Investigators with a revised informed consent/assent form.

Prior to participating in any study-related procedure, each patient must sign and date an IRB/EC-approved informed consent/assent form written in a language the patient can understand. The informed consent/assent form should be as nontechnical as practical and understandable to the patient. The informed consent/assent form must provide the patient with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The informed consent/assent form details the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. Before informed consent/assent is obtained, the patient should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the patient.

Once signed, the original informed consent/assent form will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent/assent discussion must be noted in the patient's case history. All patients will receive a copy of their signed and dated informed consent/assent form.

If the informed consent/assent form is revised during the study and requires the patient to be re-consented/re-assented, informed consent/assent will be obtained in the same manner as for the original informed consent/assent form.

11.5. Confidentiality

All information provided by Harmony Biosciences, LLC and all data and information generated by the site as part of the study will be kept confidential by the Investigator and site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study and will not be released to any unauthorized third party without prior written approval of the Sponsor. These restrictions do not apply to: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an IRB solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study patient, or 4) study results that may be published as described in Section 12.5. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement, provided, however, that the confidentiality provisions in any written contract shall not be less restrictive than this statement.

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of patients' health information. The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA) and in a form satisfactory to the Sponsor.

The patient's contact information will be securely stored at each clinical site for internal use during the study. Throughout the study, a patient's source data will only be linked to the Sponsor's clinical study database or documentation via a unique ID number. Copies of any patient source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., patient name, address, and other identifier fields not

collected in the patient's eCRF). At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the IRB and institutional regulations.

To comply with ICH guidelines for cGCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs to review the patient's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization by the patient as part of the informed consent/assent process (Section 11.4).

12. STUDY ADMINISTRATION

12.1. Clinical Monitoring

The Sponsor (or its designee) is responsible for ensuring the proper conduct of the study. This includes ensuring the patients' rights and well-being are protected, the conduct of the study is within compliance of an approved protocol and cGCPs, and integrity of the data (i.e., data are accurate, complete, and verifiable from source documentation). At regular intervals during the study, the Sponsor's study monitors, or their designees, will contact the study site via site visits, TCs, emails, and letters in order to review study progress and eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: patients' informed consent/assent documents, patient recruitment procedures, patients' compliance with study procedures, source-data verification, drug source documents, and record retention.

In the event monitoring of source data by monitors cannot be completed on site, monitoring of source data may be completed remotely.

Each study site will maintain study documents and records as specified in ICH E6, Section 8 (Essential Documents for the Conduct of a Clinical Trial) and as required by regulatory and institutional requirements. These include, but are not limited to: study protocol, eCRF, delegation of authority log, pharmacy dispensing records, drug accountability logs, AE reports, patient source data (original or certified copies), correspondence with health authorities and IRB/ECs, informed consent/assent forms, monitoring visit logs, laboratory certification or quality control procedures, and laboratory reference ranges. Access to study documents and records will be strictly controlled (Section 11.5).

Study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or if agreed to in the Clinical Trial Agreement. It is the responsibility of the Sponsor to inform the site as to when these documents no longer need to be retained.

12.2. Management of Protocol Amendments and Deviations

12.2.1. Protocol Modification

The protocol cannot be modified except in a formal protocol amendment by the Sponsor.

12.2.2. Protocol Violations and Deviations

Protocol deviations are a change, divergence, or departure from the study design or procedures defined in this protocol. An important protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. The Investigator will notify the IRB of any protocol deviations as required by IRB guidelines and site requirements. Protocol deviations will be documented at the site and in the Sponsor files. In the event of an important protocol

deviation, the site will notify the Sponsor or designee. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, as required.

12.3. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as required to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

12.4. Suspension or Termination of Study or Investigational Site

12.4.1. Suspension of Study

The Sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate.

12.4.2. Termination of Study or Investigational Site

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s). Reasons for terminating the study early or closing a site include, but are not limited to:

- Discovery of an unexpected, significant, or unacceptable risk to the patients
- Failure of the Investigator to comply with the protocol, cGCP regulations and guidelines, or local requirements
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- Data are not sufficiently complete and/or evaluable
- Sponsor decision

If the study is terminated early by the Sponsor, written notification documenting the reason for study termination will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the IRB and provide the reason(s) for study termination.

12.5. Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a patient's medical records) are the sole property of Harmony Biosciences, LLC.

For clinical interventional studies in patients, Harmony Biosciences will post study results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and EU reporting rules. Regardless of study outcome, Harmony Biosciences commits to submit for publication results of its interventional clinical studies according to the prespecified

plans for data analysis. Wherever possible, Harmony Biosciences also plans to submit for publication the results of any nonclinical or technology studies while protecting any proprietary information.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Harmony has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors, the Consolidated Standards of Reporting Trials (CONSORT) group and Good Publication Practice. A copy of this policy will be made available to the Investigator upon request.

When the study is completed or prematurely terminated, the Sponsor or designee will ensure a Clinical Study Report is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required. When required by applicable regulations, an Investigator signatory will be identified for the approval of the Clinical Study Report. The Investigator will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete study results.

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APPENDIX A. MAXIMUM ALLOWABLE BLOOD DRAW VOLUMES

This information is consistent with the National Institutes of Health (NIH) Pediatric Blood Volume for Research Guidelines (Howie 2011).

PATIENT'S WEIGHT		PATIENTS TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW
Kg	**lbs**	**mL**	**2.5% of total blood volume**
1	2.2	100	2.5
2	4.4	200	5
3	6.6	240	6
4	8.8	320	8
5	11	400	10
6	13.2	480	12
7	15.4	560	14
8	17.6	640	16
9	19.8	720	18
10	22	800	20
11 thru 15	24 thru 33	880-1200	22-30
16 thru 20	35 thru 44	1280-1600	32-40
21 thru 25	46 thru 55	1680-2000	42-50
26 thru 30	57 thru 66	2080-2400	52-60
31 thru 35	68 thru 77	2480-2800	62-70
36 thru 40	79 thru 88	2880-3200	72-80
41 thru 45	90 thru 99	3280-3600	82-90
46 thru 50	101 thru 110	3680-4000	92-100
51 thru 55	112 thru 121	4080-4400	102-110
56 thru 60	123 thru 132	4480-4800	112-120
61 thru 65	134 thru 143	4880-5200	122-130
66 thru 70	145 thru 154	5280-5600	132-140
71 thru 75	156 thru 165	5680-6000	142-150
76 thru 80	167 thru 176	6080-6400	152-160
81 thru 85	178 thru 187	6480-6800	162-170
86 thru 90	189 thru 198	6880-7200	172-180
91 thru 95	200 thru 209	7280-7600	182-190
96 thru 100	211 thru 220	7680-8000	192-200

Chart based on blood volume of:

1 to 2 kg	100 mL/kg	(pre-term infant)
>2 kg	80 mL/kg	(term infant - adult)

Daily maximum: 3 mL/kg/day maximum. If doing more than one draw per day, be careful to not exceed the one time maximum OR the daily maximum 3.0 mL/kg per day.

The amount of blood that can be drawn in a 24-hour period is the same as the maximum amount column.

Patients admitted for a solid organ transplant (pre-transplant) are expected to exceed this volume. For all other patients, physician approval is required if maximum volume is to be exceeded for a one-time draw or daily maximum.

This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by Seattle Children's Hospital Laboratory April 2012, Seattle, WA.

Rev. 11/2018

APPENDIX B. STUDY DIARY: PATIENT PITOLISANT STUDY DRUG DOSING AND SLEEP DIARY

Appendix C. EXAMPLES OF STRONG CYP2D6 INHIBITORS, STRONG CYP3A4 INDUCERS, MEDICATIONS THAT PROLONG QT INTERVAL, AND CENTRALLY ACTING H_1 RECEPTOR ANTAGONISTS

Medication Type	Examples
Strong CYP2D6 inhibitors	paroxetine, fluoxetine, bupropion, quinidine, terbinafine
Strong CYP3A4 inducers	rifampin, carbamazepine, phenytoin, apalutamide, St John's wort, enzalutamide, mitotane
Medications that prolong QT interval	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol, dofetilide Antipsychotics: ziprasidone, chlorpromazine, thioridazine, haloperidol Antibiotics: moxifloxacin, ciprofloxacin, erythromycin, ketoconazole
H_1 receptor antagonists	pheniramine maleate, diphenhydramine, promethazine (anti-histamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants

CYP = cytochrome P450

Appendix D. EPWORTH SLEEPINESS SCALE FOR CHILDREN AND ADOLESCENTS (ESS-CHAD [PARENT/CAREGIVER VERSION])

Appendix E. CAREGIVER GLOBAL IMPRESSIONS OF SEVERITY (CaGI-S) FOR EXCESSIVE DAYTIME SLEEPINESS

Please choose the response below that best describes your child's (care recipient's) **likelihood of falling asleep during daytime activities** over the past week:

□ 0 = Not at all

□ 1 = Slight likelihood

□ 2 = Moderate likelihood

□ 3 = High likelihood

□ 4 = Very high likelihood

APPENDIX F. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF OVERALL CLINICAL STATUS

Considering your total clinical experience with this particular population, please rate the patient's condition at this time. Check one:

□ 1 = Normal

□ 2 = Mildly symptomatic

□ 3 = Moderately symptomatic

□ 4 = Severely symptomatic

APPENDIX G. ABERRANT BEHAVIOR CHECKLIST-COMMUNITY, SECOND EDITION (ABC-C)

APPENDIX H. MONTEFIORE-EINSTEIN RIGIDITY SCALE – REVISED FOR RESEARCH STUDIES IN PWS (MERS-R-PWS)

APPENDIX I. 22-ITEM ZARIT BURDEN INTERVIEW (ZBI-22)

APPENDIX J. HYPERPHAGIA QUESTIONNAIRE FOR CLINICAL TRIALS (HQ-CT)

Source: McCandless SE, Yanovski JA, Mille J, et al. Effects of MetAP2 inhibition on hyperphagia and body weight in Prader-Willi syndrome: a randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2017; 19(12):1751-61.

APPENDIX K. FOOD SAFE ZONE QUESTIONNAIRE (FSZQ)

Appendix L. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) VERY YOUNG CHILD/COGNITIVELY IMPAIRED-LIFETIME RECENT

APPENDIX M. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) VERY YOUNG CHILD/COGNITIVELY IMPAIRED-SINCE LAST CONTACT

APPENDIX N. ANXIETY, DEPRESSION, AND MOOD SCALE (ADAMS)