Official Title of Study: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia

NCT Number: NCT05156047

Protocol Date (last revision date): May 18, 2023

CLINICAL STUDY PROTOCOL: HBS-101-CL-010

Protocol Title:	A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia
Investigational Product:	Pitolisant (also referred to as HBS-101)
Phase of Development:	3
Sponsor:	Harmony Biosciences, LLC 630 W. Germantown Pike, Suite 215 Plymouth Meeting, PA 19462 USA
Medical Monitor(s):	[redacted]
Medical Project Leader:	[redacted]
Operational Lead:	[redacted]
Protocol Amendment #	4
Version/Effective Date:	Version 5.0 18 May 2023

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SPONSOR SIGNATURE

Protocol Title: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia

Protocol Number: HBS-101-CL-010

This protocol (Amendment 4, Version 5.0) has been reviewed and approved by the Sponsor.

Signature: [redacted] Date: [redacted]

[redacted]

Harmony Biosciences, LLC
630 W. Germantown Pike, Suite 215
Plymouth Meeting, PA 19462
USA
[redacted]

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HBS-101-CL-010

TITLE: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia

I have received and read the current Investigator's Brochure for pitolisant. I have read the HBS-101-CL-010 protocol (Amendment 4, Version 5.0) 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-010
PHASE OF DEVELOPMENT:	3
PROTOCOL TITLE: A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia	
NUMBER OF PLANNED SUBJECTS: Open-Label Phase: Approximately 200 patients. Double-Blind Randomized Withdrawal Phase: Approximately 128 patients.	
STUDY SITES: Approximately 60 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 idiopathic hypersomnia (IH) age ≥18 years.

Key Secondary Objectives

Key secondary objectives of this study are to assess the impact of pitolisant on:

- Overall symptoms of IH
- Patient impression of overall change in their symptoms of IH
- Investigator assessment of overall disease severity of IH

Other Secondary Objectives

Other secondary objectives of this study are to assess the impact of pitolisant in patients with IH on:

- Patient impression of overall severity of their EDS
- Functional status and activities of daily living
- Sleep-related impairment
- Sleep inertia
- Cognitive function

Pharmacokinetic Objectives

The PK objectives of this study are to:

- Describe the serum concentrations of pitolisant and its major inactive metabolite (BP1.3484) in patients with IH
- Evaluate whether there is an exposure-response relationship for pitolisant in the treatment of EDS in patients with IH

METHODOLOGY:

This is a double-blind, placebo-controlled, randomized withdrawal study in adult patients (ages ≥18 years) with IH. The study will consist of a Screening Period (up to 28 days), an 8-week Open-Label Phase, and a 4-week Double-Blind Randomized Withdrawal Phase.

After completion of the Screening Period, eligible patients will be enrolled in the Open-Label Phase of the study. The Open-Label Phase of the study will be 8 weeks, which includes a 6-week Dose Optimization Period and a 2-week Stable Dose Period. In the Dose Optimization Period, all patients will be titrated to their optimal dose of open-label pitolisant (17.8 mg or 35.6 mg) based on Investigator assessment of tolerability and efficacy. Patients will take their first dose of open-label pitolisant (8.9 mg) on Day 1 and will be titrated to their optimal dose, based on tolerability and efficacy (17.8 mg or 35.6 mg pitolisant), over the first 3 weeks of the 6-week Dose Optimization Period, based on Investigator assessment of tolerability and efficacy (dose titrations will occur on Day 8 [± 2 days] and Day 15 [± 2 days]). During titration weeks (weeks 1-3), patients may remain on a lower dose for longer than 1 week or may switch between doses (higher or lower) based on Investigator assessment of tolerability and efficacy; however, the target optimal dose at the end of the 3 weeks of titration is 17.8 mg or 35.6 mg pitolisant. Patients taking a strong CYP2D6 inhibitor will be allowed in the study; however, for these patients, the maximum permitted daily dose of pitolisant will be 17.8 mg. The 3-week titration period will be followed by 3 weeks of flexible dosing (weeks 4-6) during which patients will continue to receive their optimal dose of 17.8 mg or 35.6 mg open-label pitolisant. Dose adjustments to 17.8 mg or 35.6 mg are allowed during weeks 4-6 based on Investigator assessment of tolerability and efficacy.

Following completion of the 6-week Dose Optimization Period, patients will enter the 2-week Stable Dose Period of the Open-Label Phase (weeks 7 and 8). During this period, patients will remain at their optimal dose (the same dose they were taking at the end of the Dose Optimization Period [17.8 mg or 35.6 mg]) of open-label pitolisant for 2 weeks; dose adjustments are not allowed during the Stable Dose Period. At the end of the Stable Dose Period (which is also the end of the Open-Label Phase), safety, efficacy, pharmacokinetic (PK), and genotype assessments will be collected, and patients will be defined as responders or non-responders. [redacted] Responders will be randomized in a 1:1 ratio to receive blinded study drug (pitolisant or matching placebo) in the Double-Blind Randomized Withdrawal Phase of the study. Non-responders will not be randomized to treatment in the Double-Blind Randomized Withdrawal Phase and will complete two safety follow-up telephone contacts (TCs) at 15 (±3) days and 30 (+3) days after their final dose of open-label pitolisant, which will include assessment for adverse events (AEs) and concomitant medication use. The Patient Global Impression of Change for EDS will be administered at the end of the Open-Label Phase.

During the Double-Blind Randomized Withdrawal Phase, patients (approximately 64 patients per treatment group) will receive blinded study drug at the same dose they were taking in the Stable Dose Period (17.8 mg or 35.6 mg pitolisant or matching placebo). The duration of the Double-Blind Randomized Withdrawal Phase will be 4 weeks (weeks 9-12); dose adjustments are not permitted during this phase of the study. Safety and efficacy assessments will be conducted two weeks after randomization (start of Week 11) and safety, efficacy, and PK assessments will be conducted at the end of the Double-Blind Randomized Withdrawal Phase (end of Week 12). After completion of the Double-Blind Randomized Withdrawal Phase (End-of-Treatment [EOT] Visit is on Day 84, the last day of blinded treatment), patients will complete two safety follow-up TCs with the site at 15 (±3) days and 30 (+3) days after their final dose of blinded study drug, which will include assessment for AEs and concomitant medication use; patients will also have the opportunity to enroll in a long-term, open-label safety study under a separate protocol. The Patient Cognitive and Meaningful Change Interview will be conducted at the EOT visit after completing safety and efficacy assessments and/or procedures.

STUDY POPULATION:

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.
2. Has a current diagnosis of IH per International Classification of Sleep Disorders Third Edition (ICSD-3) criteria.
3. Male or female patient age ≥18 years at the time of Screening.
4. [redacted]
5. [redacted]
6. For patients being treated for obstructive sleep apnea (OSA) or other hypoventilatory conditions, patients must be compliant as demonstrated by bilevel positive airway pressure (BiPAP)/continuous positive airway pressure (CPAP) therapy with 30 days of data showing ≥4 hours of BiPAP/CPAP therapy per night for ≥70% of nights. If not on BiPAP/CPAP therapy, patients being treated for OSA must be compliant as determined by the Investigator with their medical device or oral appliance. Data must be from within 90 days prior to the Screening visit. Patients must maintain OSA treatment compliance throughout the study.
7. If on a treatment that could affect daytime sleepiness (including but not limited to oxybates, stimulants, modafinil, and armodafinil):
    a. Must be on a stable dose for at least 2 months prior to Screening and agree to continue the stable dose for the duration of the study.
    b. If not on a stable dose for 2 months prior to Screening, washout for 5 half-lives or 14 days, whichever is longer, prior to Day 1 and agree to remain off these treatments until completion of the study.
8. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test at the Baseline Visit (Visit 2) and at the end of the Stable Dose Period (Visit 4) and agree to remain abstinent or use an effective method of non-hormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
9. Must have a negative result on urine drug screen at the Screening Visit, Baseline Visit (Visit 2) and at the end of the Stable Dose Period (Visit 4), except for medications that are prescribed by a healthcare provider for medical conditions.
10. In the opinion of the Investigator, the patient is capable of understanding and complying with 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 this study:

1. Has hypersomnia due to another medical disorder (e.g., narcolepsy).
2. Has an Apnea Hypopnea Index (AHI) of ≥10 as determined by the most recent sleep study or BiPAP/CPAP device readout.
3. Has a clinically significant hypoventilatory condition as determined by the Investigator.

4. Has a primary diagnosis of psychiatric illness that is not well controlled.
5. Patients taking antidepressants who have not been on a stable dose of their antidepressant for at least 12 weeks prior to Screening; patients on a stable dose of their antidepressant for at least 12 weeks prior to Screening must agree to continue their stable dose for the duration of the study.
6. Experiences a mean of <6 hours of sleep per night based on sleep diary during Screening (patients need to record at least 7 nights within a 10-day period in their sleep diary within 14-days prior to the Baseline Visit [Visit 2]).
7. 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 study.
8. Does not agree to discontinue any prohibited medication or substance listed in the protocol.
9. Is currently using or has previously used pitolisant.
10. 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 and for 21 days after final dose of study drug.
11. Participation in an interventional research study involving another investigational medication, device, or behavioral treatment within 28 days or within 5 half-lives of the investigational medication (whichever is longer) prior to Screening.
12. Has a diagnosis of end-stage renal disease (ESRD) (estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).
13. 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 at any time during the study.
14. Has a history of long corrected QT interval (QTc) syndrome or corrected QT interval using Fridericia's formula (QTcF) >450 msec for males or >470 msec for females (QTcF = QT / 3√ RR) at Screening.
15. Is receiving and is unable to discontinue a medication known to prolong the QT interval.
16. Is receiving a concomitant medication that is known to be a strong cytochrome P450 (CYP) 3A4 inducer or a centrally acting histamine 1 (H_1) receptor antagonist; patients who undergo a washout of these medications of at least 5 half-lives or one week (whichever is longer) may be enrolled in the study. Use of strong CYP2D6 inhibitors is allowed; however, for these patients the maximum permitted daily dose of pitolisant is 17.8 mg.
17. Is a known CYP2D6 poor metabolizer (PM).
18. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.
19. Has initiated any new or change in allied health therapies or interventions that can interfere with the study outcomes within 28 days prior to Screening and at any time during the study, based on the Investigator's judgment.

20. Has a current or recent (within 1 year) history of a substance use disorder or dependence disorder, including alcohol, tobacco, and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).
21. Has planned surgery during the study.
22. Has a significant risk of committing suicide or suicidality based on history; routine psychiatric examination; Investigator's judgment; or an answer of "yes" on any question other than questions 1 to 3 (for the previous month) or "yes" on any question in the suicidal behavior section (for the past year) of the Columbia-Suicide Severity Rating Scale (C-SSRS), Baseline/Screening.
23. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to an unstable or uncontrolled medical condition or one 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. This exclusion criterion applies not only to entry into the study, but also to continuation in the study, should such an unstable, uncontrolled, or serious medical condition arise.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Pitolisant will be provided as 4.45 mg and 17.8 mg tablets. Pitolisant will be administered orally as a single dose once daily in the morning upon wakening.

Open-Label Phase: Pitolisant will be administered as a single dose of 8.9 mg, 17.8 mg, or 35.6 mg during Weeks 1 to 3 (titration) and 17.8 mg or 35.6 mg during weeks 4 to 6 of the Dose Optimization Period. Pitolisant will be administered as a single dose of 17.8 mg or 35.6 mg during weeks 7 and 8 (Stable Dose Period).

Double-Blind Randomized Withdrawal Phase: Pitolisant will be administered as a single dose of 17.8 mg or 35.6 mg.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Placebo will be provided as matching 17.8 mg tablets in the Double-Blind Randomized Withdrawal Phase, administered orally as a single dose once daily in the morning upon wakening.

DURATION OF TREATMENT:

The duration of participation for individual patients is expected to be up to approximately 4 months for non-responders (including a maximum of 28 days of screening, 8 weeks of open-label treatment and 30 days of safety follow-up) and up to approximately 5 months for responders (including a maximum of 28 days of screening, 8 weeks of open-label treatment, 4 weeks of double-blind treatment, and 30 days of safety follow-up).

STUDY ASSESSMENTS:

Efficacy Assessments:

Efficacy will be evaluated using the ESS; Idiopathic Hypersomnia Severity Scale (IHSS); Patient Global Impression of Change for symptoms of Idiopathic Hypersomnia (PGI-C [IH]); Clinical Global Impression of Severity (CGI-S); Patient Global Impression of Severity for EDS (PGI-S); Functional Outcomes of Sleep Questionnaire 10 item version (FOSQ-10); Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment (PROMIS-SRI); Sleep Inertia Questionnaire (SIQ); and Cogstate Computerized Cognitive Test battery. Except for the Cogstate Computerized Cognitive Test battery, all efficacy assessments completed by the patient will be collected

using an electronic handheld device provided to each patient. The CGI-S will be collected using an electronic device (i.e., computer tablet) provided to each site.

Patients will undergo efficacy assessments at Screening (Visit 1; ESS and PGI-S only), Baseline (Visit 2, Day-1; all efficacy assessments except for PGI-C [IH]), Visit 3 (Day 22; ESS and CGI-S only), end of the Stable Dose Period (Visit 4, Day 56; all efficacy assessments except for PGI-C [IH]), TC 7 (all efficacy assessments except for the Cogstate Computerized Cognitive Test battery), and at the end of the Double-Blind Randomized Withdrawal Phase (Visit 5, Day 84; EOT Visit; all efficacy assessments). Additionally, the ESS will be administered at all TCs during the study.

Safety Assessments:

Safety will be assessed by monitoring and recording all AEs from the time of signing the informed consent form (ICF) through the final safety follow-up TC at 30 (+3) days after the final dose of study drug (end of the Open-Label Phase for patients who are non-responders and end of the Double-Blind Randomized Withdrawal Phase for patients who are responders). Assessment of suicide risk and suicidality will be assessed using the C-SSRS at every on-site study visit and TC during the study. Measurement of laboratory parameters (i.e., hematology, serum chemistry, and urinalysis) will be collected at every on-site study visit except for Visit 3. Vital signs will be performed at every on-site study visit. Concomitant medications will be reviewed at every on-site study visit and TC during the study. Electrocardiograms (ECGs) and full physical examinations will be performed at Screening, Day 56 (Visit 4) and Day 84 (Visit 5).

Pharmacokinetic Assessments:

Blood samples for PK assessments will be collected at the Week 8 (Visit 4) and Week 12 (Visit 5) visits at the same time as those collected for clinical laboratory evaluations. A blood sample for CYP2D6 genotype will also be collected at Visit 4. The exact time of blood sample collection for PK assessments will be recorded. On Day 50 (TC 6) and Day 71 (TC 7), patients will be reminded to record in their dosing diary the date, exact time, and dose on the morning of their Week 8 (Visit 4) and Week 12 (Visit 5) visits, respectively.

STUDY ENDPOINTS:

Efficacy Endpoints:

Primary efficacy endpoint:

- The primary efficacy endpoint is the change in ESS score from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

Key secondary efficacy endpoints:

- Change on the IHSS from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Percent of patients who worsen on the PGI-C (IH) at the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Change on the CGI-S from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

Other secondary endpoints include the change from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo for:

- PGI-S
- FOSQ-10
- PROMIS-SRI

- SIQ
- Working memory as measured by the Cogstate One Back test
- Attention as measured by the Cogstate Identification test
- Psychomotor function as measured by the Cogstate Detection test

Safety Endpoints:

Incidence of AEs, changes in clinical laboratory results and vital signs, C-SSRS assessment, 12-lead ECG results, and changes in physical examination findings.

Pharmacokinetic Endpoints:

- Summary of serum concentrations of pitolisant and BP1.3484 during specific intervals after dosing (0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, >24 h after the last dose)
- Population PK parameters of pitolisant, to be reported separately
- Exposure-response of pitolisant-induced changes in ESS, if evident, to be reported separately

STATISTICAL METHODS:

Determination of Sample Size:

The sample size in the Double-Blind Randomized Withdrawal Phase of the study is 128 patients randomized in a 1:1 ratio to one of two treatment groups (optimal dose of pitolisant [17.8 mg or 35.6 mg] or placebo). These estimates are based on the feasibility of enrollment and the goal of achieving statistically significant results for the effect of pitolisant on the symptom of EDS in patients with IH. The sample size is powered to show statistical significance.

The primary endpoint will be the change in ESS score from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo. [redacted] Approximately 200 patients are planned for enrollment in the Open-Label Phase to achieve approximately 128 responder patients to be entered into the Double-Blind Randomized Withdrawal Phase of the study.

Efficacy Analyses:

Summary statistics (mean, standard deviation [SD], median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the end of the Stable Dose Period to the end of the Double-Blind Randomized Withdrawal Phase for the active treatment group and the placebo group. The change from end of the Stable Dosing Period (i.e., Visit 4) will be analyzed in an analysis of covariance (ANCOVA) model. Fixed effects will be included for treatment, end of Stable Dose Period value, and site. Least square means (LSMs), standard errors, and the LSM differences will be reported. Missing values will be imputed using multiple imputation (MI) using a composite approach. Patients who withdraw for AEs or lack of effect will be assumed to be missing not at random and will have values imputed based on the baseline (pre-titration) values. Intermittent missing values and values for patients who withdrawal for other reasons will be imputed assuming they are missing at random and will be based on values from their randomized treatment group from the same time point, conditioned on their non-missing values, including baseline and end of Stable Dose Period.

Safety Analyses:

All safety data will be tabulated and listed. Adverse events, ECG abnormalities, and other categorical outcomes will be summarized with counts and percentages. Continuous outcomes will be reported using summary statistics.

[redacted]

[redacted]

Pharmacokinetic Analysis:

Serum concentrations of pitolisant and BP1.3484 will be listed and summarized by specific intervals after dosing (0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, >24 h after the last dose). Concentrations of pitolisant may be combined with data from other studies using the same bioanalytical method to describe the population PK parameters of pitolisant. The methodology will be reported in a separate analysis plan and the results will be reported in a separate population PK report. Exploratory plots may be produced to evaluate whether there is a relationship between exposure (predicted C_{max}, AUC_{tau}, C_{trough}) and response to pitolisant based on ESS. If an exposure-response relationship is evident from plots, an exposure-response model may be developed and reported in the population PK report.

SCHEDULE OF ASSESSMENTS (SOA)

	Screening Period		Open-Label Phase									Double-Blind Randomized Withdrawal Phase[b]				
			Dose Optimization Period[a] Weeks 1 to 6 (Day 1 to 42)						Stable Dose Period[b] Weeks 7 to 8 (Day 43 to 56)			Weeks 9 to 12 (Day 57 to 84)				
			W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8		W 9	W 11	W 12		
Visit/TC Study Day	VISIT 1 Day -28 to -2	Baseline[c] VISIT 2 Day -1	Day 1[d]	TC1 Day 8 (±2d)	TC2 Day 15 (±2d)	VISIT 3 Day 22 (±2d)	TC3 Day 29 (±2d)	TC4 Day 36 (±2d)	TC5[e] Day 43 (±2d)	TC6[e] Day 50 (±2d)	VISIT 4[f] Day 56 (±3d)	Day 57[g] (±3d)	TC7[e] Day 71 (±3d)	EOT[h]/ ET[i] VISIT 5 Day 84 (±3d)	Safety F-Up TCs[j]	Unsch Visit[k]
Informed consent	X															
Assess/confirm eligibility	X	X									X					
Demographics	X															
Medical history	X															
Determination of AHI[l]	X															
Pregnancy test (FCBP)[m]	X	X				X					X			X		
Urine drug screen	X	X									X			X		
Physical examination[n]	X	X				X					X			X		
Body weight	X	X									X			X		
Height	X															
Vital signs[o]	X	X				X					X			X		
Clinical laboratory tests	X	X									X			X		
Blood sample for PK[p]											X			X		
Blood sample for CYP2D6 genotype[p]											X					
12-lead ECG[q]	X										X			X		

	Screening Period		Open-Label Phase									Double-Blind Randomized Withdrawal Phase[b]				
			Dose Optimization Period[a] Weeks 1 to 6 (Day 1 to 42)						Stable Dose Period[b] Weeks 7 to 8 (Day 43 to 56)			Weeks 9 to 12 (Day 57 to 84)				
			W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8		W 9	W 11	W 12		
Visit/TC Study Day	VISIT 1 Day -28 to -2	Baseline[c] VISIT 2 Day -1	Day 1[d]	TC1 Day 8 (±2d)	TC2 Day 15 (±2d)	VISIT 3 Day 22 (±2d)	TC3 Day 29 (±2d)	TC4 Day 36 (±2d)	TC5[e] Day 43 (±2d)	TC6[e] Day 50 (±2d)	VISIT 4[f] Day 56 (±3d)	Day 57[g] (±3d)	TC7[e] Day 71 (±3d)	EOT[h]/ ET[i] VISIT 5 Day 84 (±3d)	Safety F-Up TCs[j]	Unsch Visit[k]
C-SSRS	X	X		X	X	X	X	X	X	X	X		X	X		
Adverse events[r]	X	X		X	X	X	X	X	X	X	X		X	X	X	X
Concomitant medication	X	X		X	X	X	X	X	X	X	X		X	X	X	X
Sleep diary[s]	X								X	X						
Randomization											X					
Dispense study drug		X				X					X					
Study drug dosing diary[t]		X														
Administer/ Titrate study drug			X	X	X	X	X	X	X	X	X[u]	X	X	X		
Study drug compliance/ accountability				X	X	X	X	X	X	X	X		X	X		X
ESS	X	X		X[v]	X[v]	X	X[v]	X[v]	X[v]	X[v]	X[w]		X[v]	X		
PGI-S	X	X									X		X	X		
IHSS		X									X		X	X		
PGI-C (IH)													X	X		
CGI-S		X				X					X		X	X		
FOSQ-10		X									X		X	X		
PROMIS-SRI		X									X		X	X		
SIQ		X									X		X	X		

Visit/TC Study Day	Screening Period		Open-Label Phase									Double-Blind Randomized Withdrawal Phase[b]			Safety F-Up TCs[j]	Unsch Visit[k]
			Dose Optimization Period[a] Weeks 1 to 6 (Day 1 to 42)						Stable Dose Period[b] Weeks 7 to 8 (Day 43 to 56)			Weeks 9 to 12 (Day 57 to 84)				
			W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8		W 9	W 11	W 12		
	VISIT 1 Day -28 to -2	Baseline[c] VISIT 2 Day -1	Day 1[d]	TC1 Day 8 (±2d)	TC2 Day 15 (±2d)	VISIT 3 Day 22 (±2d)	TC3 Day 29 (±2d)	TC4 Day 36 (±2d)	TC5[e] Day 43 (±2d)	TC6[e] Day 50 (±2d)	VISIT 4[f] Day 56 (±3d)	Day 57[g] (±3d)	TC7[e] Day 71 (±3d)	EOT[h]/ ET[i] VISIT 5 Day 84 (±3d)		
Cogstate One Back		X[x]									X			X		
Cogstate Identification		X[x]									X			X		
Cogstate Detection		X[x]									X			X		
PGI-C (EDS)											X					
Patient Cognitive and Meaningful Change Exit Interview														X[y]		

Abbreviations: AE = adverse event; AHI = Apnea Hypoxia Index; BiPAP = bilevel positive airway pressure; CGI-S = Clinical Global Impression of Severity; CPAP = continuous positive airway pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; d=day; ECG = electrocardiogram; EOT = end-of-treatment; ET = early termination; ESS = Epworth Sleepiness Scale; ET = early termination; FCBP = female of childbearing potential; FOSQ-10 = Functional Outcomes of Sleep Questionnaire 10 item version; F-Up = follow-up; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; OSA = obstructive sleep apnea; PGI-C (IH) = Patient Global Impression of Change for symptoms of IH; PGI-C (EDS) = Patient Global Impression of Change for Excessive Daytime Sleepiness; PGI-S = Patient Global Impression of Severity; PROMIS-SRI = Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment; SIQ = Sleep Inertia Questionnaire; TC = telephone contact; Unsch = unscheduled; W=week.

[a] Patients will take their first dose of open-label pitolisant on Day 1 and will be titrated to their optimal dose (17.8 mg or 35.6 mg pitolisant) during weeks 1 to 3 of the 6-week Dose Optimization Period, based on Investigator assessment of tolerability and efficacy (Table 5). The 3 weeks of titration will be followed by 3 weeks of flexible dosing (weeks 4-6) during which patients will continue to receive their optimal dose of 17.8 mg or 35.6 mg open-label pitolisant. Patients must be taking at least 17.8 mg pitolisant daily to enter the Stable Dose Period. Tolerability and efficacy will be assessed weekly at TCs and an onsite study visit (Visit 3).

[b] Dose adjustments are not permitted during the 2-week Stable Dose Period and the 4-week Double-Blind Randomized Withdrawal Phase.

[c] Eligible patients will be dispensed open-label pitolisant at Visit 2 and will be instructed to take their first dose of open-label pitolisant on the following day in the morning upon wakening (on Day 1).

[d] First day of open-label dosing; there is no TC or study visit scheduled for this day.

[e] On Day 43 (TC 5) and Day 50 (TC 6), patients will be reminded to record sleep diary data in their electronic provisioned handheld device for approximately 7 days prior to their Week 8 visit (Visit 4). On Day 50 (TC 6) and Day 71 (TC 7), patients will be reminded to record in their dosing diary using their electronic provisioned handheld device the date, exact time, and dose on the morning of their Week 8 (Visit 4) and Week 12 (Visit 5) visits, respectively.

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[g] First day of blinded dosing; there is no TC or study visit scheduled for this day.
[h] Visit 5 (Day 84 ±3 days) is the EOT Visit for the Double-Blind Randomized Withdrawal Phase. Visit 5 should be performed at the same time of day as Visit 4. Patients who complete the Double-Blind Randomized Withdrawal Phase of the study will have the opportunity to enroll in a long-term, open-label safety study under a separate protocol.
[i] Patients who prematurely discontinue study drug are required to complete the ET visit. Reasons for discontinuation must be recorded.
[j] Patients who choose not to enroll in the optional a long-term, open-label safety study under a separate protocol will receive two Safety Follow-up TCs from the study site, one at 15 (±3) days and the second at 30 (+3) days after their final dose of study treatment to assess for AEs which will include assessment for adverse events (AEs) and concomitant medication use.
[k] Unscheduled visits and assessments may be conducted by TC or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator as detailed in Section 7.7.
[l] If previously diagnosed with OSA and treatment with BiPAP or CPAP was prescribed, the Investigator will obtain from the patient a download of BiPAP/CPAP therapy data with 30 days of data showing ≥4 hours of BiPAP/CPAP therapy per night for at least 70% of nights. AHI is determined by the most recent sleep study or BiPAP/CPAP device readout.
[m] Serum pregnancy test is to be performed at Screening and a urine pregnancy test is to be performed at all other visits (Visits 2, 3, 4, and 5), as indicated.
[n] Full physical examination is to be performed at Screening, Visit 4, and Visit 5; an abbreviated physical examination is to be performed at Visit 2 and Visit 3.
[o] 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.
[p] Blood samples for PK assessment will be collected at the same time as those collected for clinical laboratory evaluations. The exact dose and time of collection will be recorded. At Visit 4, a blood sample for CYP2D6 genotype will also be collected.
[q] Perform ECGs after the patient has been resting for at least 5 minutes, prior to any blood draws at Visits 1, 4, and 5.
[r] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 days (+3 days) after final dose of study drug. At the safety follow-up TCs, AEs and concomitant medication use will be recorded (Section 7.6).
[s] Patients will be instructed to record their sleep time in their sleep diary. Patients must have a mean of at least 6 hours of sleep per night for at least 7 nights during the Screening Period to be eligible for the study (patients need to record at least 7 nights in their sleep diary within a 10-day period prior to the Baseline Visit [Visit 2]). The mean should be taken from all days recorded in the patient's sleep diary. At TC 5 and TC 6 patients will be reminded to record sleep diary data in their electronic provisioned handheld device for approximately 7 days prior to their Visit 4 (Week 8).
[t] Patients will be instructed to start recording daily study drug dosing information using their electronic provisioned handheld device. The electronic study drug dosing diary will be used to record the number of tablets administered daily, including date, time of administration, and dose taken. The study drug dosing diary will be used for the duration of a patient's participation in the study.
[u] Eligible patients will be instructed to take blinded study drug once daily in the morning upon wakening starting on the day after completing Visit 4 (Day 56).
[v] At all TCs, the ESS is to be administered by designated site staff who are trained in administration of the assessment.
[w] [redacted]
[x] To familiarize patients with the Cogstate Computerized Cognitive Test battery, the test battery is to be administered three times during Visit 2, with a break of at least 15 minutes between the second test battery and the third test battery; the first and second test batteries will be considered the practice test batteries and the third test battery will be used as the Baseline assessment.
[y] If not feasible to conduct interview at Visit 5, then the interview can be scheduled up to 3 days after Visit 5.

Assessments associated with on-site study visits may be completed remotely or at an alternative location, under the oversight of the Investigator, as detailed in Section 6.5.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AASM	American Academy of Sleep Medicine
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AHI	Apnea Hypopnea Index
ANCOVA	Analysis of covariance
ASP	Average sleep propensity
BiPAP	Bilevel Positive Airway Pressure
CGI-S	Clinical Global Impression of Severity
cGCP	Current Good Clinical Practice
CNS	Central nervous system
CPAP	Continuous Positive Airway Pressure
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
eGFR	Estimated glomerular filtration rate
EOT	End-of-Treatment
ESRD	End-stage renal disease
ESS	Epworth Sleepiness Scale
ET	Early Termination
EU	European Union
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration

FOSQ	Functional Outcomes of Sleep Questionnaire
FOSQ-10	Functional Outcomes of Sleep Questionnaire 10 item version
GCP	Good Clinical Practice
H_1R	Histamine 1 receptor
H_3	Histamine 3
H_3R	Histamine 3 receptor
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders Third Edition
ID	Identification
IH	Idiopathic hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
ITT	Intent-to-treat
IRB	Institutional Review Board
IRT	Interactive response technology
LOE	Lack of effect
LSM	Least square mean
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MI	Multiple imputation
MOA	Mechanism of action
MSLT	Mean Sleep Latency Test
NDA	New drug application
NT1	Narcolepsy type 1
NT2	Narcolepsy type 2
PGI-C (EDS)	Patient Global Impression of Change for EDS
PGI-C (IH)	Patient Global Impression of Change for symptoms of IH
PGI-S	Patient Global Impression of Severity

PROMIS-SRI	Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment
PSG	Polysomnography
OSA	Obstructive sleep apnea
PK	Pharmacokinetic
PM	Poor metabolizer
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
REM	Rapid eye movement
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIQ	Sleep Inertia Questionnaire
SOP	Standard operating procedure
SOREM	Sleep-onset rapid eye movement
TC	Telephone contact
TEAE	Treatment-emergent adverse event
TMN	Tuberomammillary nucleus
US	United States
USP	United States Pharmacopeia

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

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Section Number		

INTRODUCTION

1.1. Background Information and Study Rationale

Central disorders of hypersomnolence are rare, chronic, neurological disorders that are primarily characterized by excessive daytime sleepiness (EDS). The three primary central disorders of hypersomnolence include narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) (AASM 2014). These disorders are typically caused by abnormalities in the central nervous system (CNS) that control sleep-wake states (Sateia 2014). Idiopathic hypersomnia is characterized by hypersomnolence, with EDS being the cardinal symptom, despite normal or prolonged sleep (Arnulf et al 2019). Other symptoms of IH include:

- High sleep inertia or "sleep drunkenness", which is a pronounced period of confusion and sleepiness upon wakening (Trotti 2017a)
- "Brain fog", which is an inability to think clearly or concentrate at any time throughout the day (Trotti et al 2020b)
- Cognitive dysfunction, including working memory and attention issues, along with compromised alertness (Saini and Rye 2017)

Other clinical features of IH may include sleep paralysis, hallucinations, nightmares, headache, migraine, pain, fatigue, depression, mood changes, and neurovegetative symptoms (Kahn and Trotti 2015; Vernet 2009; Vernet et al 2010). From a clinical perspective, significant overlap exists between IH and narcolepsy symptoms; however, IH and narcolepsy can be differentiated diagnostically based on the number of sleep onset rapid eye movement (SOREM) periods on a multiple sleep latency test (MSLT) and the presence or absence of cataplexy. The approximate age of onset of the symptoms of IH is late teens, however a diagnosis of IH is often not established until a patient reaches their mid-30s (Ali et al 2009; Anderson et al 2007). A diagnosis of IH is based on clinical history in combination with objective sleep testing (i.e., MSLT, polysomnography [PSG], or actigraphy) as well as exclusion of other causes of EDS (Landzberg and Trotti 2019).

The prevalence of IH in the general population is not as well understood as that for narcolepsy due to a lack of population-based epidemiological studies (Sowa 2016), but it is generally considered less prevalent than narcolepsy (Perez-Carbonell and Leschziner 2018). Based on the US population of 330 million (US Census Bureau 2021) and an approximate 0.01%-0.05% prevalence rate for IH (Acquavella et al 2020; Sowa 2016; Kahn and Trotti 2015), the general US population-based prevalence estimate of IH is approximately 33,000 to 165,000 people.

Idiopathic hypersomnia is characterized by EDS, which is defined as "daily episodes of an irrepressible need to sleep or daytime lapses into sleep" (AASM 2014; Sateia 2014). In IH, EDS is paradoxically unrelated to the amount of sleep obtained. Patients with IH report that their sleep is disturbed and not restorative; however, when measured with PSG their sleep architecture appears normal and reveals high sleep efficiency, low arousal indices, and appropriate quantities of both rapid eye movement (REM) and non-REM sleep (Arnulf et al 2019). Sleep length among persons with IH appears to be within a typical range, if not longer (Vernet et al 2009). Within the ICSD Second Edition (ICSD-2), IH diagnostic criteria were differentiated in subclassifications of IH with long sleep and IH without long sleep. Long sleep is defined as >600 minutes of mean

daily sleep time (ICSD-2). The ICSD-3 removed this subclassification from the IH diagnostic criteria because there was insufficient scientific evidence to support a clear dichotomous diagnostic classification (Sateia 2014). Additionally, patients with IH tend to have an evening chronotype (i.e., most active and alert in the evening), do not show a delayed sleep phase syndrome, but may have a longer circadian period that could explain the high levels of sleep inertia following waking from sleep (Vernet et al 2009; Landzberg and Trotti 2019). Sleep inertia is a difficulty waking after sleep and is present in most patients with IH (Landzberg and Trotti 2019; Trotti et al 2020b; Trotti 2017; Vernet et al 2009). The objectively measured sleep profile among patients with IH appears normal, which is inconsistent with their subjective reports of EDS, their subjective reports that their sleep is not restorative, and their experience of sleep inertia upon waking.

The burden of IH results in decreased quality of life for the individual, and it carries social and economic impacts as well. In a large community-based sample, people with IH reported worse quality of life, with greater sleepiness and fatigue when compared with healthy controls (Miglis et al 2020). Among people with IH, greater daytime sleepiness is associated with worse quality of life overall as well as in specific domains that include relationships, perceived support from others, and autonomy in controlling work schedule (Ozaki et al 2012). Furthermore, people with IH report deficits in working memory and attention, compromised alertness during situations that require focus, and being in a persistent state of "brain fog" that impairs day-to-day activities (Vernet et al 2010; Saini and Rye 2017).

Idiopathic hypersomnia has no known single pathophysiological cause. Proposed hypotheses regarding the underlying causes of IH include alterations of key sleep-wake regulatory pathways (i.e., histamine, hypocretin, GABAergic and monoaminergic), sleep-wake instability, disrupted sleep homeostasis, circadian rhythm dysfunction, dysfunction of the autonomic nervous system, alterations to the brain's default mode network, differences in brain structure and connectivity, and potential alterations in cerebral blood flow (Kanbayashi et al 2009; Thorpy 2019; Rye et al 2012; Billiard et al 2016; Sforza et al 2016; Boucetta et al 2017; Dauvilliers et al 2017; Arnulf et al 2019; Landzberg and Trotti 2019; Pomares et al 2019). Whether each of these mechanisms contribute to, or are a result of, EDS in patients with IH is currently unknown.

The symptoms of IH are generally long lasting; however, their burden can be mitigated by effective long-term treatments (Pizza et al 2015; Trotti et al 2020b). Prior to August 2021, no medications were approved by the FDA for the treatment of IH. Therefore, people with IH have relied on non-pharmacological approaches, medications used off-label, or a combination of both, to manage their disorder (Morgenthaler et al 2007). These methods have been investigated for efficacy with mixed and inconsistent results. Non-pharmacological approaches to manage IH include daytime naps, scheduled nocturnal sleep, caffeine, nicotine, diet, exercise, temperature manipulation, chewing gum, mindfulness, and yoga (Neikrug et al 2017). However, evidence for effective non-pharmacological interventions is lacking (Schinkelshoek et al 2019).

Recommendations for pharmacological approaches to manage IH symptoms have been established by the American Academy of Sleep Medicine (AASM) in their 2021 clinical practice guidelines for the treatment of central disorders of hypersomnolence (Maski et al 2021a). The AASM provided a "strong" recommendation (i.e., "we recommend") for modafinil, and "conditional" recommendations (i.e., "we suggest") for pitolisant, clarithromycin, methylphenidate, and sodium oxybate. The recommendation for pitolisant was based on one

retrospective, observational study of pitolisant for IH, which demonstrated clinically significant improvement in EDS (Leu-Semenescu et al 2014). Although the overall quality of evidence was considered very low, based on their clinical expertise, the AASM Task Force determined that the benefit-risk profile of pitolisant use in patients with IH "probably favors the use of pitolisant" (Maski et al 2021a). Additional treatments that are currently used for the treatment of IH but were not included in the 2021 guidelines include amphetamines (i.e., methamphetamine and dextroamphetamine), armodafinil, solriamfetol, flumazenil, melatonin, methylprednisolone, and lithium (Trotti and Arnulf 2020a). Given the similar profiles of IH and NT2 (Maski et al 2021b), current treatments for IH are similar to those used for narcolepsy. In a letter to the FDA, thought leaders in disorders of hypersomnia have called for the research and development of therapeutic agents aimed at treating the full range of symptoms specific to IH (Hypersomnia Foundation 2015).

WAKIX® (pitolisant) is currently approved in the United Stated (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 Canada, Israel, Norway, South Korea, Switzerland, and the United Kingdom. Pitolisant is a first-in-class, potent, and highly selective histamine 3 receptor (H_3R) antagonist/inverse agonist with a novel mechanism of action (MOA). It binds to H_3Rs and blocks the normal negative feedback mechanism for histamine release, resulting in increased release of histamine, a wake-promoting neurotransmitter. It also functions as an inverse agonist, resulting in enhanced histamine synthesis and release from presynaptic neurons. Pitolisant is well-absorbed after oral administration and easily crosses the blood-brain barrier so that after low oral doses, it elicits histamine release in the CNS.

Pitolisant triggers the release of histamine and long-lasting activation of histaminergic neurons in the brain, a neuronal system involved in the maintenance of wakefulness (Scammell et al 2017; Scammell et al 2019). Pitolisant also increases release of other neurotransmitters (including dopamine, norepinephrine, serotonin, and acetylcholine), via H_3 heteroreceptors within those neuronal systems, which can have an impact on sleep/wake regulation and cognitive function (Robbins and Roberts 2007; Millan et al 2016; Scammell et al 2017; Scammell et al 2019). Importantly, pitolisant does not result in an increase of dopamine release in the striatum, including the nucleus accumbens (a region central to the neural reward network), which differentiates pitolisant from other wake-promoting agents' abuse liability (i.e., psychostimulants) (New Drug Application [NDA] 211150, Section 2.4.1.4; Uguen et al 2013).

The posterior hypothalamic tuberomammillary nucleus (TMN) is the histamine-producing region of the brain, and its axons project widely throughout the brain, innervating and activating neurons in the preoptic area, prefrontal cortex, neocortex, and striatum. Near the TMN are hypocretin (orexin)-producing neurons, whose axons project to and activate histaminergic neurons (Scammell et al 2019). Both hypocretin (orexin) and histamine work by stabilizing wakefulness through inhibition of REM sleep-promoting neurons, inhibition of non-REM sleep-promoting neurons, and activation of wake-promoting neurons.

Excessive daytime sleepiness is a symptom that is common among neurological disorders; however, whether the underlying cause of EDS is similar across disease states, and if drugs effective in alleviating EDS in one disease state will be effective for alleviating EDS in another disease state, remains unclear. Psychostimulant drugs (i.e., modafinil and methylphenidate)

approved for the treatment of EDS in narcolepsy are effectively used off label in some patients with IH (Bastuji and Jouvet 1988; Anderson et al 2007; Ali et al 2009; Lavault et al 2011); however, controlled clinical trials to determine the safety and efficacy of these medications for treating EDS in these patients are lacking. A body of research has investigated histamine levels in the cerebral spinal fluid (CSF) from patients with IH and has yielded mixed results. Most note that patients with IH do not have low histamine levels in CSF compared with normal controls (e.g., Trotti and Arnulf 2020a). However, Kanbayashi and colleagues (2009) demonstrated that non-medicated patients with IH had significantly lower CSF histamine levels compared with a healthy control sample whereas medicated patients with IH who were taking CNS stimulants and antidepressants did not. Low levels of CNS histamine may therefore be a nonspecific marker of hypersomnolence rather than a causal mechanism in IH. Nevertheless, CNS histamine is a key neurotransmitter in sleep-wake regulation and has shown promise as a potential treatment for patients with IH (Evangelista et al 2018; Trotti and Arnulf 2020a).

The MOA of pitolisant in triggering activation of histaminergic neurons in the brain that results in increased release of histamine strongly supports the rationale for evaluation of pitolisant in the domains of sleepiness, cognition, and sleepiness-related impairment in patients with IH. A retrospective chart review of patients with IH who were treated with pitolisant during a 3-year period from a single center in France found that patients treated with pitolisant exhibited statistically significant improvements in EDS (Leu-Semenescu et al 2014) [redacted]

To date, no clinical studies have been conducted in the US to evaluate pitolisant in patients with IH. Based on its unique MOA, pitolisant presents a novel approach to the management of EDS and other symptoms in patients with IH. Given the recognized adjacency and phenotypic similarities between IH and narcolepsy, pitolisant could potentially provide a favorable treatment option for these patients. This Phase 3 study will evaluate the impact of pitolisant on EDS, sleep inertia, cognitive function, and the overall impact of these symptoms on daily functioning in adult patients with IH.

1.2. Rationale for Study Design

This double-blind, placebo-controlled, Phase 3 study will evaluate the safety and efficacy of pitolisant compared with placebo in adult patients with IH (ages ≥18 years) utilizing a randomized withdrawal design. The randomized withdrawal design employs an enrichment strategy designed to exclude patients unlikely to demonstrate clinical benefit; only patients who respond to a given intervention (i.e., responders) are studied in the double-blind phase. The successful intervention is terminated, and patients are randomized to either an active or placebo arm of the study. This study design provides a study population that has demonstrated that the therapeutic intervention can be effective, and subsequent significant differences between the active and placebo groups during the Double-Blind Randomized Withdrawal Phase would demonstrate efficacy of the active treatment.

The study will consist of an 8-week Open-Label Phase, which includes a 6-week Dose Optimization Period followed by a 2-week Stable Dose Period. During the Dose Optimization Period, patients will be titrated to their optimal dose (i.e., 17.8 mg or 35.6 mg pitolisant, based on tolerability and efficacy) prior to entering the 2-week Stable Dose Period (dose adjustments are

not permitted during the Stable Dose Period). [redacted]

The primary efficacy endpoint in the study is the change in ESS score from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

Secondary efficacy endpoints will evaluate the effect of pitolisant on other symptoms of IH, including overall burden of disease, sleep-related impairment, sleep inertia, and cognitive function. The scales and measures used to evaluate the secondary endpoints are described in Section 6.2

1.3. Dose Rationale

The dosing regimen for this study is 17.8 mg or 35.6 mg pitolisant (based on tolerability and efficacy) administered once daily in the morning upon wakening and is consistent with the current FDA-approved prescribing information for WAKIX® (pitolisant) for the treatment of EDS or cataplexy in adult patients with narcolepsy.

1.4. Potential Risks and Benefits

The overall safety/tolerability profile of pitolisant at doses of 4.45 mg 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 (OSA), Parkinson's disease, epilepsy, schizophrenia, Lewy body dementia, and attention deficit hyperactivity disorder (ADHD) (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 adverse events (TEAEs) in patients who received pitolisant in the Phase 2/3 studies (N=1513) 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 is contraindicated in patients with severe hepatic impairment, and pitolisant is not recommended in patients with end-stage renal disease (ESRD). 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. To mitigate potential cardiovascular (CV) risks in this study, patients with potential for QT prolongation and patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers (PMs) are excluded from participation. Patients with ESRD, moderate or severe hepatic impairment, or moderate or severe renal impairment are also excluded.

There has been 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. These studies also showed that pitolisant was well tolerated when used concomitantly with other common narcolepsy treatments, including modafinil, methylphenidate, sodium oxybate, and venlafaxine. There were no clinically relevant effects of pitolisant on vital signs, electrocardiogram (ECG) parameters, or laboratory findings across the clinical development safety database. Additional information is provided in the current WAKIX (pitolisant) Investigator's Brochure (IB) and current FDA-approved 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 IH age ≥18 years.

2.2. Secondary Objectives

The key secondary objectives of this study are to assess the impact of pitolisant on:

- Overall symptoms of IH
- Patient impression of overall change in their symptoms of IH
- Investigator assessment of overall disease severity of IH

Other secondary objectives of this study are to assess the impact of pitolisant in patients with IH on:

- Patient impression of overall severity of their EDS
- Functional status and activities of daily living
- Sleep-related impairment
- Sleep inertia
- Cognitive function

2.3. Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are:

- Determine the serum concentrations of pitolisant and its major inactive metabolite (BP1.3484) in patients with IH
- Evaluate whether there is an exposure-response relationship for pitolisant in the treatment of EDS in patients with IH

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a double-blind, placebo-controlled, randomized withdrawal study in adult patients (ages ≥18 years) with IH. The study will consist of a Screening Period (up to 28 days), an 8-week Open-Label Phase, and a 4-week Double-Blind Randomized Withdrawal Phase. An overall schematic of the study design is provided in Figure 1.

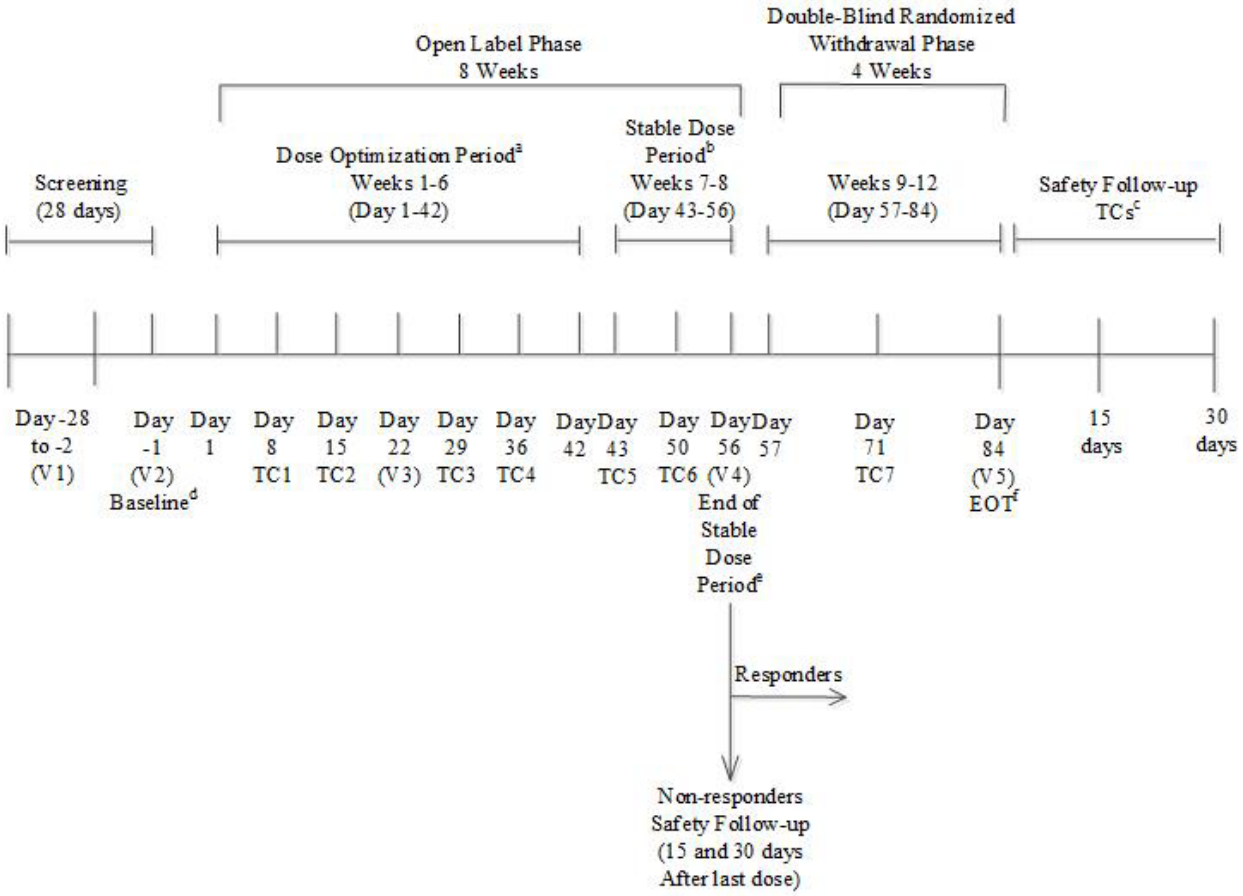
After completion of the Screening Period, approximately 200 patients ages ≥18 years who meet all eligibility criteria will be enrolled in the Open-Label Phase of the study. The duration of the Open-Label Phase of the study will be 8 weeks, including a 6-week Dose Optimization Period and a 2-week Stable Dose Period. In the Dose Optimization Period, all patients will be titrated to their optimal dose of open-label pitolisant (17.8 mg or 35.6 mg) based on Investigator assessment of tolerability and efficacy. Patients taking a strong CYP2D6 inhibitor will be allowed in the study; however, for these patients, the maximum permitted daily dose of pitolisant will be 17.8 mg (Section 3.1.3.1). Following completion of the Dose Optimization Period, patients will enter the 2-week Stable Dose Period of the Open-Label Phase. During this period, patients will remain at their optimal dose (17.8 mg or 35.6 mg) of open-label pitolisant for 2 weeks; dose adjustments are not allowed during this Stable Dose Period (Section 3.1.3.2).

[redacted]

During the Double-Blind Randomized Withdrawal Phase, approximately 128 patients (approximately 64 per treatment group) will receive blinded study drug at the same dose they were taking in the Stable Dose Period (17.8 mg or 35.6 mg pitolisant or matching placebo) (Section 3.1.4). The duration of the Double-Blind Randomized Withdrawal Phase will be 4 weeks; dose adjustments are not permitted in this phase of the study.

Further details on the Screening Period are provided in Section 3.1.2. Further details for the Open-Label Phase and Double-Blind Randomized Withdrawal Phase (including safety and efficacy evaluations) of the study are provided in Section 3.1.3 and Section 3.1.4, respectively.

Figure 1: Overall Study Design



Abbreviations: AE = adverse event; EOT = end-of-treatment; ESS = Epworth Sleepiness scale; TC = telephone contact; V = visit.

[a] Patients will take their first dose of open-label pitolisant on Day 1 and will be titrated to their optimal dose (17.8 mg or 35.6 mg pitolisant), during weeks 1 to 3 of the 6-week Dose Optimization Period, based on Investigator assessment of tolerability and efficacy. For patients taking a strong CYP2D6 inhibitor, the maximum permitted daily dose of pitolisant is 17.8 mg (Section 3.1.3.1). The 3 weeks of titration will be followed by 3 weeks of flexible dosing (weeks 4-6) during which patients will continue to receive their optimal dose of 17.8 mg or 35.6 mg open-label pitolisant.
[b] In the Stable Dose Period, patients will continue to take open-label pitolisant at the same dose they were taking at the end of the Dose Optimization Period (17.8 mg or 35.6 mg) for 2 weeks (weeks 7 and 8) as detailed in Section 3.1.3.2. Dose adjustments are not permitted during the Stable Dose Period.
[c] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 days (+3 days) after final dose of study drug; AEs and concomitant medication use will be recorded (Section 7.6).
[d] Eligible patients will be dispensed open-label pitolisant at Visit 2 (Baseline) and will be instructed to take their first dose on the following day (Day 1) in the morning upon wakening, as detailed in Section 3.1.2.2.
[e] All patients will complete all assessments scheduled for Visit 4 (end of the Stable Dose Period; Day 56) as detailed in Section 7.3.2.2. [redacted] Patients who complete the Double-Blind Randomized Withdrawal Phase will have the opportunity to enroll in a long-term, open-label safety study under a separate protocol.

3.1.2. Screening and Baseline Visits

3.1.2.1. Screening (Visit 1)

The Screening Period will be a maximum of 28 days. At the Screening Visit (Visit 1), after written informed consent is provided, patients will undergo screening assessments. Patients will be provided with an electronic handheld device that includes a sleep diary (Appendix A) to record their daily sleep activity. Patients will record their sleep time in the morning. Patients must have a mean of at least 6 hours of sleep per night for at least 7 nights during the Screening Period to be eligible for the study (patients need to record at least 7 nights in their sleep diary within at least a 10-day period prior to the Baseline Visit [Visit 2]). The mean should be taken from all days recorded in the patient's sleep diary.

For patients being treated for OSA, screening will also include assessment of Apnea Hypopnea Index (AHI) based on bilevel positive airway pressure (BiPAP)/continuous positive airway pressure (CPAP) data. Patients with an AHI of ≥10 will be excluded. Patients must also be compliant with BiPAP/CPAP therapy as demonstrated by 30 days of data showing ≥4 hours of BiPAP/CPAP therapy per night for at least 70% of nights. If not on BiPAP/CPAP therapy, patients being treated for OSA must be compliant as determined by the Investigator with their medical device or oral appliance. Data must be from within 90 days of the Screening visit.

Patients who meet all of the eligibility requirements will be enrolled in the study.

3.1.2.2. Baseline Visit (Visit 2)

At the Baseline Visit (Day -1), patients who continue to meet eligibility criteria will complete all scheduled assessments (Section 7.2), will be dispensed open-label pitolisant, and will be instructed to complete a study drug dosing diary (an example of the study drug dosing diary is provided in Appendix B).

Patients will be instructed to take open-label pitolisant once daily in the morning upon wakening. Patients will record the number of tablets taken daily and the date and time of administration in their study drug dosing diary using their electronic provisioned handheld device. Patients will complete their study drug dosing diary daily for the duration of their participation in the study.

Patients will be instructed to begin taking open-label pitolisant on the day after the Baseline Visit as detailed in Section 3.1.3; the first day of study drug administration is Day 1.

3.1.3. Open-Label Phase (8 Weeks)

3.1.3.1. Dose Optimization Period (6 Weeks)

Patients will take their first dose of open-label pitolisant (8.9 mg) on Day 1 (the day after the Baseline Visit) and will be titrated to their optimal dose (17.8 or 35.6 mg pitolisant) over the first 3 weeks of the 6-week Dose Optimization Period, based on Investigator assessment of tolerability and efficacy. The titration schedule for dosing is presented in Table 5 (pitolisant dose will be titrated on Day 8 [± 2 days] and again on Day 15 [± 2 days]). During titration (weeks 1-3), patients may remain on a lower dose for longer than 1 week or may switch between doses (higher or lower) based on Investigator assessment of tolerability and efficacy; however, the target optimal dose at the end of the 3 weeks of titration is 17.8 mg or 35.6 mg pitolisant. For

patients taking a strong CYP2D6 inhibitor, the maximum permitted daily dose of pitolisant is 17.8 mg. The 3 weeks of titration will be followed by 3 weeks of flexible dosing during which patients will continue to receive their optimal dose of 17.8 mg or 35.6 mg open-label pitolisant; dose adjustments to 17.8 mg or 35.6 mg are allowed during weeks 4-6 based on Investigator assessment of tolerability and efficacy.

Table 5: Pitolisant Dosing in the 6-Week Dose Optimization Period

Titration[a] (3 weeks)			Flexible Dosing[b] (3 weeks)
Week 1 (Days 1-7)	**Week 2 (Days 8-14)**	**Week 3 (Days 15-21)**	**Weeks 4-6 (Days 22-42)**
8.9 mg	17.8 mg	35.6 mg	17.8 mg or 35.6 mg

[a] Patients may remain on a lower dose of pitolisant for longer than 1 week or switch between doses (higher or lower) based on Investigator assessment of tolerability and efficacy during weeks 1 to 3 of the Dose Optimization Period. Minimum permitted dose after Week 3 is 17.8 mg. For patients taking a strong CYP2D6 inhibitor, the maximum permitted daily dose of pitolisant is 17.8 mg.

[b] Patients must be taking 17.8 mg or 35.6 mg pitolisant during weeks 4 to 6; dose adjustments to 17.8 mg or 35.6 mg are allowed based on Investigator assessment of tolerability and efficacy.

During the Dose-Optimization Period, patients will be contacted weekly by the study site by telephone; telephone contacts (TCs) will be on Day 8 (TC 1), Day 15 (TC 2), Day 29 (TC 3), and Day 36 (TC 4), and an on-site visit (Visit 3) will be completed on Day 22. At all TCs and the on-site visit (Visit 3), tolerability and efficacy will be assessed by AE and concomitant medication monitoring and completion of the Columbia-Suicide Severity Rating Scale (C-SSRS) and ESS. At Visit 3 (Day 29), the Clinical Global Impression of Severity (CGI-S) will also be completed.

3.1.3.2. Stable Dose Period

Following the 6-week Dose Optimization Period, patients will continue to take open-label pitolisant at their optimal dose (the same dose they were taking at the end of the Dose Optimization Period [17.8 mg or 35.6 mg]) once daily in the morning upon wakening for 2 weeks (days 43-56) in the Stable Dose Period. Dose adjustments are not permitted during the 2-week Stable Dose Period.

During the Stable Dose Period, patients will receive a TC from the site on Day 43 (TC 5) and Day 50 (TC 6) during which tolerability and efficacy will be assessed by AE and concomitant medication monitoring and completion of the C-SSRS and ESS. During TC 5 and TC 6, patients will be reminded to record sleep diary data in their electronic provisioned handheld device for approximately 7 days prior to their next clinic visit (Visit 4). In addition, on Day 50 (TC 6) patients will be reminded to record in their dosing diary the date, exact time, and dose on the morning of their Week 8 visit (Visit 4).





At Visit 4, all patients (responders and non-responders) will complete all of the scheduled safety, PK, CYP2D6 genotype, and efficacy assessments (Section 7.3.2.2).

Patients who are defined as responders at the end of the Stable Dose Period (Visit 4) but no longer meet eligibility criteria for the study will not be randomized to treatment in the Double-Blind Randomized Withdrawal Phase of the study. These patients will receive two Safety Follow-up TCs from the study site, one at 15 (±3) days and the second at 30 (+3) days after their final dose of open-label pitolisant to assess for AEs and concomitant medication use as detailed in Section 7.6.

3.1.4. Double-Blind Randomized Withdrawal Phase

Eligible patients who are assessed as responders at the end of the Stable Dose Period (Section 3.1.3.2) will be randomized at a 1:1 ratio to receive pitolisant or matching placebo in the Double-Blind Randomized Withdrawal Phase of the study. Patients randomized to pitolisant will receive pitolisant at the same dose they were taking at the end of the Stable Dose Period (17.8 mg or 35.6 mg).

Patients will take their first dose of blinded study drug (17.8 mg or 35.6 mg pitolisant or matching placebo) on Day 57 (the first day of blinded treatment) and will continue to take study drug once daily in the morning upon wakening for 4 weeks (days 57-84). Dose adjustments are not permitted during the Double-Blind Randomized Withdrawal Phase of the study.

During the Double-Blind Randomized Withdrawal Phase, patients will receive a TC from the study site on Day 71 (TC 7) to assess efficacy (ESS; Patient Global Impression of Severity [PGI-S]; Idiopathic Hypersomnia Severity Scale [IHSS]; Patient Global Impression of Change [PGI-C [IH]]; CGI-S; Functional Outcomes of Sleep Questionnaire 10 item version [FOSQ-10]; Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment (PROMIS-SRI); and Sleep Inertia Questionnaire [SIQ]) and tolerability (AEs, concomitant medication monitoring, and C-SSRS). In addition, on Day 71 (TC 7) patients will be reminded to record in their dosing diary the date, exact time, and dose on the morning of their Week 12 visit (Visit 5) using their electronic provisioned handheld device.

The End-of-Treatment (EOT) Visit (Visit 5) is on Day 84 (the last day of blinded treatment); efficacy, PK, and tolerability assessments for the EOT Visit are outlined in Section 7.4.2. The Patient Cognitive and Meaningful Change Interview will be conducted at Visit 5 after completing safety and efficacy assessments and/or procedures. After completing the EOT Visit, patients will receive two Safety Follow-up TCs from the study site, one at 15 (±3) days and the second at 30 (+3) days after the final dose of blinded study drug to assess for AEs and concomitant medications (Section 7.6).

Patients who complete the Double-Blind Randomized Withdrawal Phase of the study will have the opportunity to enroll in a long-term, open-label safety study under a separate protocol.

3.1.5. Dose Adjustments

Adjustments to open-label pitolisant dose are permitted during the 6-week Dose Optimization Period of the Open-Label Phase (Section 3.1.3.1). Discussions and decisions regarding adjustments in pitolisant dose will occur over the telephone or during on-site study visits (either scheduled or unscheduled) and will be based on Investigator assessment of tolerability and efficacy.

Dose adjustments are not permitted during the Stable Dose Period or during the Double-Blind Randomized Withdrawal Phase of the study.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in ESS score from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

3.2.1.2. Secondary Efficacy Endpoints

Key secondary efficacy endpoints:

- Change on the IHSS from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Percent of patients who worsen on the PGI-C (IH) at the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- The change on the CGI-S from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

Other secondary endpoints include the change from the end of the Stable Dose Period (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo for:

- PGI-S
- FOSQ-10
- PROMIS-SRI
- SIQ
- Working memory as measured by the Cogstate One Back test
- Attention as measured by the Cogstate Identification test
- Psychomotor function as measured by the Cogstate Detection test

3.2.2. Safety Endpoints

Safety will be assessed by monitoring the incidence of AEs and changes in clinical laboratory test results, vital signs, C-SSRS assessment, 12-lead ECG results, and physical examination findings from signing of informed consent through 30 days after final dose of study drug (end of Open-Label Phase for non-responders and end of Double-Blind Randomized Withdrawal Phase for responders).

3.2.3. Pharmacokinetic Endpoints

- Summary of serum concentrations of pitolisant and BP1.3484 during specific intervals after dosing (0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, >24 h after the last dose)
- Population PK parameters of pitolisant, to be reported separately
- Exposure-response of pitolisant-induced changes in ESS, if evident, to be reported separately

3.3. Study Duration

The duration of participation for individual patients is up to approximately 4 months for non-responders (including a maximum of 28 days of screening, 8 weeks of open-label treatment and 30 days of safety follow-up) and up to approximately 5 months for responders (including a maximum of 28 days of screening, 8 weeks of open-label treatment, 4 weeks of double-blind treatment, and 30 days of safety follow-up).

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 200 patients are planned for enrollment in the Open-Label Phase to achieve 128 responder patients to be entered into the Double-Blind Randomized Withdrawal Phase of the study. Patients will be enrolled in the study at approximately 60 sites in the US.

4.1.1. Inclusion Criteria

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

1. Is able to provide voluntary, written informed consent.
2. Has a current diagnosis of IH per International Classification of Sleep Disorders Third Edition (ICSD-3) criteria.
3. Male or female patient age ≥18 years at the time of Screening.

[redacted]

6. For patients being treated for OSA or other hypoventilatory conditions, patients must be compliant as demonstrated by BiPAP/CPAP therapy with 30 days of data showing ≥4 hours of BiPAP/CPAP therapy per night for ≥70% of nights. If not on BiPAP/CPAP therapy, patients being treated for OSA must be compliant as determined by the Investigator with their medical device or oral appliance. Data must be from within 90 days prior to the Screening visit. Patients must agree to maintain compliance with their treatment for OSA throughout the duration of the study.
7. If on a treatment that could affect daytime sleepiness (including but not limited to oxybates, stimulants, modafinil, and armodafinil):
    a. Must be on a stable dose for at least 2 months prior to Screening and agree to continue the stable dose for the duration of the study.
    b. If not on a stable dose for 2 months prior to Screening, washout for 5 half-lives or 14 days, whichever is longer, prior to Day 1 and agree to remain off these treatments until completion of the study.
8. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test at the Baseline Visit (Visit 2) and at the end of the Stable Dose Period (Visit 4) and agree to remain abstinent or use an effective method of non-hormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
9. Must have a negative result on urine drug screen at the Screening Visit, Baseline Visit (Visit 2) and at the end of the Stable Dose Period (Visit 4), except for medications that are prescribed by a healthcare provider for medical conditions.
10. In the opinion of the Investigator, the patient is capable of understanding and complying with 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 hypersomnia due to another medical disorder (e.g., narcolepsy).
2. Has an AHI of ≥10 as determined by the most recent sleep study or BiPAP/CPAP device readout.
3. Has a clinically significant hypoventilatory condition as determined by the Investigator.
4. Has a primary diagnosis of a psychiatric illness that is not well controlled.
5. Patients taking antidepressants who have not been on a stable dose of their antidepressant for at least 12 weeks prior to Screening; patients on a stable dose of their antidepressant for at least 12 weeks prior to Screening must agree to continue their stable dose for the duration of the study.
6. Experiences a mean of <6 hours of sleep per night based on sleep diary during Screening (patients need to record at least 7 nights within a 10-day period in their sleep diary within 14-days prior to the Baseline Visit [Visit 2]).
7. 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 study.
8. Does not agree to discontinue any prohibited medication or substance listed in the protocol.
9. Is currently or has previously used pitolisant.
10. 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 and for 21 days after final dose of study drug.
11. Participation in an interventional research study involving another investigational medication, device, or behavioral treatment within 28 days or within 5 half-lives of the investigational medication (whichever is longer) prior to Screening.
12. Has a diagnosis of ESRD (estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).
13. 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 at any time during the study.
14. Has a history of long corrected QT interval (QTc) syndrome or corrected QT interval using Fridericia's formula (QTcF) >450 msec for males or >470 msec for females (QTcF = QT / 3√ RR) at Screening.
15. Is receiving and is unable to discontinue a medication known to prolong the QT interval.
16. Is receiving a concomitant medication that is known to be a strong CYP3A4 inducer, or a centrally acting histamine 1 (H_1) receptor antagonist; patients who undergo a washout of these medications of at least 5 half-lives or one week (whichever is longer) may be enrolled in the study. Use of strong CYP2D6 inhibitors is allowed; however, for these patients the maximum permitted daily dose of pitolisant is 17.8 mg.

17. Is a known CYP2D6 poor metabolizer (PM).
18. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.
19. Has initiated any new or change in allied health therapies or interventions that can interfere with the study outcomes within 28 days prior to Screening and at any time during the study, based on the Investigator's judgment.
20. Has a current or recent (within 1 year) history of a substance use disorder or dependence disorder, including alcohol, tobacco, and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).
21. Has planned surgery during the study.
22. Has a significant risk of committing suicide or suicidality based on history; routine psychiatric examination; Investigator's judgment; or an answer of "yes" on any question other than questions 1 to 3 (for the previous month) or "yes" on any question in the suicidal behavior section (for the past year) of the C-SSRS, Baseline/Screening.
23. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to an unstable or uncontrolled medical condition or one 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. This exclusion criterion applies not only to entry into the study, but also to continuation in the study, should such an unstable, uncontrolled, or serious medical condition arise.

4.2. Method of Assigning Patients to Treatment Groups

Patients who meet all eligibility criteria will be assigned a unique identification (ID) number prior to dosing in the Open-Label Phase using interactive response technology (IRT).

[redacted]

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 (responders) who are randomized to treatment in the Double-Blind Randomized Withdrawal Phase, entrance eligibility criteria must be confirmed before administration of blinded study drug.

4.3. Blinding

For the Double-Blind Randomized Withdrawal Phase, patients, 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 treatment assignments.

[redacted]

Blinding is not applicable in the Open-Label Phase of the study.

4.3.1. Breaking the Blind

The study blind should not be broken except for in medical emergencies when the appropriate medical management of the patient requires knowledge of the study drug they 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 the 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 one 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 decision
- Lost to follow-up
- No longer meets eligibility criteria
- Non-compliance with study protocol
- Non-compliance with study treatment
- Other, with specific reason (e.g., pregnancy)

Any ECG finding that demonstrates QT prolongation (i.e., QTcF >500 msec or an increase >60 msec regardless of resultant QTc value) should be promptly addressed by the Investigator and will require discontinuation of study drug.

Patients who develop ESRD (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.

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 C-SSRS will be discontinued and will require further evaluation by the Investigator.

4.4.2. Procedures for Patient Follow-up

Patients who complete the Open-Label Phase of the study and are defined as non-responders will complete all of the Visit 4 safety and efficacy assessments (Section 3.1.2.2) and will receive two Safety Follow-up TCs from the site, one at 15 (±3) days and the second at 30 (+3) days after their last dose of open-label pitolisant, to assess for AEs and concomitant medication use as detailed in Section 7.6.

Patients (responders) who complete the Double-Blind Randomized Withdrawal Phase of the Study will complete the EOT safety and efficacy assessments (Section 7.4.2) and will receive two Safety Follow-up TCs from the site, one at 15 (±3) days and the second at 30 (+3) days after their last dose of blinded treatment, to assess for AEs and concomitant medication use as detailed in Section 7.6. Patients who complete the Double-Blind Randomized Withdrawal Phase of the study and enroll directly in the long-term, open-label safety study (under a separate protocol) are not required to complete the Safety Follow-up TCs.

Patients who prematurely discontinue study drug in the Open-Label Phase or Double-Blind Randomized Withdrawal Phase are required to undergo the safety assessments in the Early termination (ET) Visit, and the reasons for discontinuation must be recorded (Section 7.6). Every effort should be made to educate patients on the importance of remaining in the study and attending scheduled study visits, including those required after early discontinuation of study drug.

4.4.3. Withdrawal of Consent for Follow-up

Patients 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 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 electronic case report form (eCRF).

4.4.4. Patients Deemed Lost to Follow-up

Investigators should make every effort to contact patients who are potentially lost to follow-up, including pursuing any alternative contact methods permitted by local regulations or agreed to by the patient. All attempts to contact the patient will be documented in the patient's eCRF and source notes. At a minimum, three documented attempts to contact the patient, 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 Double-Blind Randomized Withdrawal Phase of the study will not be replaced. Patients who are enrolled in the study but withdraw prior to receiving any randomized study drug may be replaced.

4.6. Study and Patient Completion

4.6.1. Study Completion

The study will be completed when the last patient completes the second Safety Follow-up TC at 30 days after final dose of blinded treatment in the Double-Blind Randomized Withdrawal Phase or enrolls in the long-term open-label safety study (under a separate protocol) after completing treatment in the Double-Blind Randomized Withdrawal Phase.

4.6.2. Patient Completion

Patients who complete the 30-day follow-up TC and patients who complete the Double-Blind Randomized Withdrawal Phase and enroll directly in the long-term open-label safety study (under a separate protocol) will be considered to have completed the study.

4.7. Screen Failures

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

Patients who fail to meet eligibility criteria at the Screening or Baseline Visits (Visit 1 and Visit 2, respectively) will be screen failed without receiving open-label pitolisant. Patients who fail screening for any reason, [redacted] may be rescreened once for enrollment in the Open-Label Phase upon Medical Monitor review and approval. If a patient is rescreened for enrollment in the Open-Label Phase, a new informed consent form (ICF) must be signed, and a new ID number will be assigned by IRT. If the patient is outside of the initial 28-day screening window, all screening procedures must be repeated.

Patients who fail to meet eligibility criteria at the end of the Stable Dose Period (Visit 4) will not be randomized and will not receive blinded study drug in the Double-Blind Randomized Withdrawal Phase. These patients may not be rescreened.

In the event a patient does not meet eligibility criteria for enrollment into the Open-Label Phase or the Double-Blind Randomized Withdrawal Phase, 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 Dose Optimization Period of the Open-Label Phase at the discretion of the Investigator as described in Section 3.1.3.1.

5.1. Description of Study Drug

5.1.1. Pitolisant (Investigational Product)

Pitolisant tablets will be provided in strengths of 4.45 mg and 17.8 mg:

- 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 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.

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 the active pitolisant film-coated tablets (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

Pitolisant for the Open-Label Phase (Dose Optimization Period and Stable Dose Period; Day 1 through Day 56) will be provided to patients as 30-count bottles containing pitolisant 4.45 mg or 17.8 mg tablets.

Study drug for the Double-Blind Randomized Withdrawal Phase (from Day 57 through Day 84) will be provided to patients as 30-count bottles containing pitolisant 17.8 mg tablets or matching placebo.

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 Open-Label Phase and Double-Blind Randomized Withdrawal Phase is described in Section 5.4.1; additional information for study drug administration is provided in a separate instructional document.

5.4.1. Study Drug Administration

In the Open-Label Phase, patients will take open-label pitolisant once daily in the morning upon wakening as detailed in Section 3.1.3.1 (Dose Optimization Period) and Section 3.1.3.2 (Stable Dose Period).

In the Double-Blind Randomized Withdrawal Phase, patients will take study drug (pitolisant or matching placebo) once daily in the morning upon wakening as detailed in Section 3.1.4.

An electronic study drug dosing diary will be used, and patients will be instructed to record the number of tablets taken and the date and time of administration daily in their study drug dosing diary.

Every effort should be made to educate patients on the importance of remaining compliant with study drug dosing. If a dose is missed during the study, the patient should take the next dose the following morning upon wakening.

5.5. Study Drug Compliance

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

Study drug compliance will be monitored by reviewing the patient study drug dosing diary in conjunction with the Investigator or designee conducting tablet counts based on the returned study drug. The patient's study drug dosing diary will be reconciled with tablet counts, and any discrepancies investigated and documented. During TCs, compliance will be monitored by confirming the current dose of study drug being taken by the patient.

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] Good Clinical Practice [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 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 and the second Safety Follow Up TC (30 +3 days after final dose of study drug, Section 7.6) 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.

For patients entering the study on a stable dose of an allowed medication (Section 5.7.1), changes in dosing during the study are not permitted unless medically necessary; if a change in dose is required, the change 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.

Except for the prohibited medications specified in Section 5.7.2, patients will be allowed to continue medication(s) for the treatment of IH or other comorbidities as currently prescribed by their physicians. Patients must agree to maintain compliance with their treatment for OSA throughout the duration of the study.

For concomitant medications administered due to an AE/serious adverse event (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.

The use of medications known to be strong CYP3A4 inducers, or centrally acting histamine 1 receptor (H_1R) antagonists is not permitted. Where applicable, these medications 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.

Examples of strong CYP3A4 inducers, centrally acting H_1R antagonists, and medications that may prolong the QT interval are provided in Appendix C.

5.7.3. Medications Requiring Adjustment to the Dose of Pitolisant

The presence of strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Use of strong CYP2D6 inhibitors is allowed during the study; however, if used, the maximum permitted

daily dose of pitolisant is 17.8 mg. Examples of strong CYP2D6 inhibitors are provided in Appendix C.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. Except for the Cogstate Computerized Cognitive Test battery, all efficacy assessments completed by the patient will be collected using an electronic handheld device provided to each patient. The CGI-S will be completed using an electronic device (i.e., computer tablet) provided to each site. Additional information about the timing of assessments is provided in Section 7 and in the Schedule of Assessments (SOA). In the event the device is not working, the site will use paper versions of the licensed questionnaires.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained at Screening to ensure patients qualify for the study and will be updated at the Baseline Visit (Visit 2) if needed and as necessary thereafter. Confirmation of a patient's diagnosis of IH per ICSD-3 criteria will be obtained via review of the patient's medical records. If available, confirmation of whether a patient is with long sleep time or without long sleep time will be collected and recorded in the eCRF.

6.1.2. Demographics

Demographic information collected will include date of birth, sex, race, and ethnicity.

6.2. Efficacy and Supportive Assessments

Efficacy will be evaluated using the ESS, IHSS, PGI-C (IH), CGI-S, PGI-S, FOSQ-10, PROMIS-SRI, SIQ, and Cogstate computerized cognitive test battery. The timing of these efficacy evaluations is presented in the SOA and in Section 7. Site personnel who administer any efficacy assessments must complete rater training prior to the initiation of screening. Raters will receive a Rater Training Certificate that documents the successful completion of rater training. Site staff should make every effort to ensure that each patient is rated by the same rater throughout the study.

6.2.1. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with eight questions in which respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing or falling asleep while engaged in eight different activities. The total ESS score (sum of 8 item scores) can range from 0 to 24; the total score gives an estimate of the person's 'average sleep propensity' (ASP), across a wide range of activities in their daily lives. The higher the ESS score, the higher that person's ASP in daily life or their 'daytime sleepiness'. The ESS is provided in Appendix D.

6.2.2. Idiopathic Hypersomnia Severity Scale (IHSS)

Assessment of the global symptoms of IH will be measured using the IHSS. The IHSS is a self-administered questionnaire with a total of 14 items that assess nighttime sleep symptoms and the related sleep inertia (5 items), daytime sleep symptoms and the related sleep inertia (4 items), and impaired daytime functioning due to hypersomnolence (5 items). All items are scored from 0 to 3 or 4, depending on severity, with an overall score ranging from 0 to 50 and higher scores

reflecting more severe and frequent symptoms. The IHSS (7-day recall version) is provided in Appendix E.

6.2.3. Patient Global Impression of Severity (PGI-S) for Excessive Daytime Sleepiness

Patient assessment of EDS will be measured using a PGI-S item at Screening, Visit 2 (Baseline Visit), Visit 4 (End-of Stable Dose Period), TC 7 (Week 11), and Visit 5 (End of Treatment).

[redacted]

6.2.4. Patient Global Impression of Change for Symptoms of IH (PGI-C [IH])

Patient assessment of change in their symptoms of IH will be measured using a PGI-C (IH) item.

[redacted]

6.2.5. Clinical Global Impression of Severity (CGI-S)

Clinician overall assessment of disease severity will be measured using the CGI-S. The CGI-S is a one-item, 5-point Likert-type rating scale and is a widely used assessment in clinical psychopharmacology trials to assess severity of illness.

[redacted]

6.2.6. Functional Outcomes of Sleep Questionnaire 10-Item Version (FOSQ-10)

The Functional Outcomes of Sleep Questionnaire (FOSQ) is a 30-item instrument that is divided into five subscales (Weaver et al 1997) and has been widely used within a variety of clinical and research populations. A shorter, 10-item, version of the FOSQ (i.e., the FOSQ-10, also referred to as the FOSQ short) was developed and validated to capture the content of the original instrument but reduce administration burden while retaining strong psychometric properties (Chasens et al 2009). The FOSQ-10 is accepted as a "valid and reliable measure for the clinical evaluation of disorders of excessive daytime sleepiness and the effectiveness of related interventions" (Chasens et al 2009) and is the version to be used in this study. The FOSQ-10 is provided in Appendix I.

6.2.7. Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment (PROMIS-SRI)

The PROMIS-SRI is a self-report measure that includes eight questions designed to assess a patient's perceptions of their waking alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness over the past week (Buysse et al 2010). The PROMIS-SRI is a

validated instrument designed to be relevant across all conditions rather than being limited to specific disorders. It has been rigorously tested for and demonstrated acceptable, reliability and validity. The PROMIS-SRI v1.0 – Short Form 8a questionnaire will be used in this study and is provided in Appendix J.

6.2.8. Sleep Inertia Questionnaire (SIQ)

The SIQ instrument specifically measures sleep inertia in clinical and research settings. The SIQ yields a total score with four subscales that include physiological, responses to sleep inertia, cognitive, and emotional assessments. Higher SIQ scores represent greater sleep inertia. The SIQ is provided in Appendix K.

6.2.9. Cogstate Computerized Cognitive Battery Tests

Cognition will be assessed using the Cogstate Computerized Cognitive Battery tests, 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 working memory, attention, and psychomotor function will be assessed using the One Back, Identification, and Detection tests, respectively. To familiarize patients with the Cogstate Computerized Cognitive Test battery, the test battery includes an initial learning module and will be administered three times during Visit 2, with a break of at least 15 minutes between the second test battery and the third test battery; the first and second test batteries will be considered the practice test batteries and the third test battery will be used as the Baseline assessment.

6.2.9.1. 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 (Lawlor-Savage and Goghari 2014) with playing card stimuli displayed on a screen. The patient is asked whether the card displayed in the center of the screen is the same as the card presented immediately prior. The patient responds by pressing the “yes” or “no” key. The software measures the speed and accuracy of each response. For speed, lower scores represent better test performance. For accuracy, higher scores represent better test performance. The duration of the test is 4 minutes.

6.2.9.2. 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). For speed, lower scores represent better test performance. For accuracy, higher scores represent better test performance. The duration of the test is 3 minutes.

6.2.9.3. 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). For speed, lower scores represent better test performance. For accuracy, higher scores represent better test performance. The duration of the test is 3 minutes.

6.2.10. Patient Global Impression of Change for EDS (PGI-C [EDS])

Patient assessment of overall change in their EDS will be measured using the PGI-C (EDS). The PGI-C (EDS) consists of two items. [redacted]

6.2.11. Patient Cognitive and Meaningful Change Interview

Patient interviews will be conducted during Visit 5 after completion of the safety and efficacy assessments and/or procedures. [redacted]

Further details are provided in a separate interview guide.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs, regardless of causality or seriousness, will be collected from the time the patient provides written informed consent through 30 days after the final dose of study drug (final Safety Follow-up TC, Section 7.6). 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.

6.3.2. Physical Examination

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 endocrine/metabolic, CV, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems. Abbreviated physical examinations will be performed based on patient-reported symptoms.

Height and weight will be measured using standardized methods. Height will be recorded at Screening (Visit 1). Body weight will be recorded at Screening (Visit 1), Baseline (Visit 2), End of Stable Dose Period (Visit 4), and EOT (Visit 5).

6.3.3. 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.

6.3.4. 12-Lead Electrocardiogram

A single 12-lead ECG will be performed at Screening (Visit 1), End of Stable Dose Period (Visit 4), and EOT (Visit 5), after the patient has been resting for at least 5 minutes and prior to any blood draws. ECGs will be recorded using the site's standard ECG equipment, will be interpreted by the investigator (or qualified designee) for clinical significance, and results will be entered into the eCRF.

Any ECG finding that demonstrates QT prolongation (i.e., QTcF >500 msec or an increase >60 msec regardless of resultant QTc value) should be promptly addressed by the Investigator and will require discontinuation of study drug (Section 4.4.1).

6.3.5. 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 6. Samples for clinical laboratory tests (serum chemistry and hematology) will be collected as outlined in Section 7.

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.

The estimated total volume of blood to be drawn on PK sampling days, including samples for PK analyses (4.0 mL per sample) and clinical laboratory tests is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period (NIH 2009).

Table 6: Clinical Laboratory Tests

Drug Screen (Urine) -Barbiturates -Cocaine metabolites -Opiates -Tetrahydrocannabinol -Phencyclidine -Methadone -Amphetamines/Stimulants -Hypnotics **Urinalysis** -Specific gravity -pH -Blood -Glucose -Protein -Leukocyte esterase -Ketones -Bilirubin -Nitrites -Casts -Crystals -Erythrocytes -Renal tubular epithelial cells -WBCs -Bacteria **Pregnancy Screen (FCBP only)** -Serum (at Screening only) -Urine (as scheduled after screening)	**Serum Chemistry** -Albumin -Alkaline phosphatase -Alanine aminotransferase -Aspartate aminotransferase -Blood urea nitrogen -Calcium -Chloride -Creatinine -Creatine kinase -Glucose -High-density lipoprotein -Low-density lipoprotein -Magnesium -Phosphorus -Potassium -Sodium -Total bilirubin -Direct bilirubin -Total cholesterol -Total protein -Triglycerides -Uric acid **Hematology** -Complete blood count, including platelet count and WBC count with differential -Hemoglobin -Hematocrit -HbA1C

FCBP=females of childbearing potential, HbA1C = hemoglobin A1C; WBC = white blood cell.

6.3.6. Columbia-Suicide Severity Rating Scale

Suicide risk and suicidality at Screening will be assessed using the C-SSRS, Baseline/Screening (for the previous month) (Appendix M). After Screening, suicidality will be evaluated at all study visits and TCs through use of the Since Last Visit C-SSRS (Appendix N). 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).

6.4. Pharmacokinetic Assessments

Blood samples for determination of pitolisant and its major metabolite (BP1.3484) concentrations will be collected at the end of the Stable Dose Period of the Open-Label Phase (Visit 4) and at the end of the Double-Blind Randomized Withdrawal Phase (Visit 5); scheduled 12-lead ECG testing will be performed before each PK sample collection. A blood sample will also be collected for CYP2D6 genotype at Visit 4. The PK and genotype samples will be collected at the same time as those collected for clinical laboratory evaluations. The exact time of collection will be recorded. On Day 50 (TC 6) and Day 71 (TC 7), patients will be reminded to record the date, exact time, and dose on the morning of their Week 8 (Visit 4) and Week 12 (Visit 5) visits, respectively.

The estimated total volume of blood to be drawn on PK sampling days, including samples for PK analyses (4.0 mL per sample) and clinical laboratory tests is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period (NIH 2009).

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

6.5. Potential Use of Alternative Methods for Completing Study Assessments

For the Screening Visit (Visit 1) and Visit 3 (Day 22 ±2 days), specific assessments may be completed by alternative methods if a patient is unable to travel to the study site. A summary of assessments that may be completed remotely by the Investigator and/or site staff using telemedicine technology and assessments that may be completed in the patient's home by a home healthcare professional includes:

- Specific safety assessments including the assessment of AEs, the review of concomitant medications, and administration of the C-SSRS may be completed by the Investigator and/or site staff remotely using telemedicine technology.
- Specific efficacy assessments including administration of the ESS, IHSS, PGI-C (IH), PGI-S, FOSQ-10, PROMIS-SRI, and SIQ may be patient self-administered under the supervision of the Investigator. The CGI-S 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.
- Other assessments including physical examination, vital signs, 12-lead ECG, clinical laboratory tests, urine drug screen, and pregnancy test may be completed in the patient's home by a home healthcare professional under the guidance and supervision of the Investigator.

Details of assessments that may be competed remotely for the Screening Visit (Visit 1) and for Visit 3 are provided in Section 6.5.1 and Section 6.5.2, respectively.

The Baseline Visit (Visit 2), Visit 4 (end of Stable Dose Period), and Visit 5 (EOT) cannot be completed remotely and must be completed at the study site.

6.5.1. Assessments that may be Completed Remotely for the Screening Visit (Visit 1)

For the Screening Visit (Visit 1), assessments that may be completed remotely by the Investigator or designee using telemedicine technology and assessments that may be completed at the patient's home by a home healthcare professional under the guidance and supervision of the Investigator are detailed in Table 7.

Table 7: Remote Assessments for the Screening Visit (Visit 1)

Assessment/Procedure	Performed via Telemedicine	Performed by a Home Healthcare Professional
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		X
C-SSRS (Baseline/Screening)	X	X
ESS	X	X
PGI-S	X	
Clinical laboratory tests		X
Urine drug screen		X
Pregnancy test (FCBP only)		X
Dispense sleep diary	X	
Adverse events	X	X
Concomitant medications	X	X

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiograph; ESS = Epworth Sleepiness Scale; FCBP = female of child-bearing potential; PGI-S = Patient Global Impression of Severity

6.5.2. Assessments that may be Completed Remotely for Visit 3

At Visit 3, assessments that may be completed remotely by the Investigator or designee using telemedicine technology or by a home healthcare professional at the patient's home under the guidance and supervision of the Investigator are detailed in Table 8.

Table 8: Remote Assessments for Visit 3

Assessment/Procedure	Performed via Telemedicine	Performed by a Home Healthcare Professional
Urine pregnancy test (FCBP only)		X
Abbreviated physical examination		X
Vital signs		X
C-SSRS (Since Last Visit)	X	X
ESS	X	X
CGI-S	X	
Adverse events	X	X
Concomitant medications	X	X
Study drug compliance	X	
Study drug accountability	X	X
Dispense study drug[a]	X	

[a] Study drug may be sent to patients per the study site standard of procedures (SOP).
CGI-S=Clinical Global Impression of Severity; C-SSRS=Columbia Suicide Severity Rating Scale; ESS = Epworth Sleepiness Scale; FCBP = female of child-bearing potential.

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 SOA.

7.1. Screening: Visit 1

After providing written informed consent, patients will undergo 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 28 days.

Patients will be provided with an electronic handheld device to complete a sleep diary (Appendix A) and will be instructed to record their sleep time during Screening. Patients need to record at least 7 nights within a 10-day period in their sleep diary within a 14-day period prior to the Baseline Visit (Visit 2).

The following evaluations will be performed during the Screening Visit (Visit 1), within 28 days prior to the first dose of open-label pitolisant:

- Inclusion/exclusion criteria (Section 4.1)
- Demographics
- Medical history (Section 6.1.1)
- For patients on treatment for OSA, determination of AHI and treatment compliance[1]
- Serum pregnancy test (FCBP only)
- Urine dug screen (Table 6)
- Full physical examination (Section 6.3.2)
- Body weight and height (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 6)
- 12-lead ECG (Section 6.3.4)
- Risk of suicide/suicidality (C-SSRS Baseline/Screening; Appendix M)
- AEs (since providing written informed consent)
- Concomitant medications (since providing written informed consent)
- ESS (Section 6.2.1)
- PGI-S (Section 6.2.3)

[1] If being treated for OSA and on BiPAP or CPAP therapy, the Investigator will obtain from the patient 30 days of data showing ≥4 hours of BiPAP/CPAP therapy per night for at least 70% of nights along with AHI data. If not on BiPAP/CPAP therapy, patients must be compliant as determined by the Investigator with their medical device or oral appliance. AHI data will be referenced from the most recent sleep study or BiPAP/CPAP device readout. Data must be from within 90 days of the Screening visit.

- Dispense electronic sleep diary

Patients who fail screening for any reason, [redacted], may be rescreened once for enrollment in the Open-Label Phase upon Medical Monitor review and approval.

7.2. Baseline: Visit 2 (Day -1)

The following assessments will be completed at Visit 2:

- Review of inclusion/exclusion criteria (patients must meet all eligibility criteria) (Section 4.1)
- Medical history update (Section 6.1.1)
- Urine pregnancy test (FCBP only)
- Urine drug screen (Table 6)
- Abbreviated physical examination (Section 6.3.2)
- Body weight (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 6)
- C-SSRS, Since Last Visit (Appendix N)
- Review of AEs (since providing written informed consent)
- Review of concomitant medications (since providing written informed consent)
- ESS (Section 6.2.1)
- PGI-S (Section 6.2.3)
- IHSS (Section 6.2.2)
- CGI-S (Section 6.2.5)
- FOSQ-10 (Section 6.2.6)
- PROMIS-SRI (Section 6.2.7)
- SIQ (Section 6.2.8)
- Cogstate Computerized Cognitive Test battery (to familiarize patients with the test, the test battery includes an initial learning module and is to be administered three times, with a break of at least 15 minutes between the second test battery and the third test battery; the first and second test batteries are considered the practice test batteries and the third test battery is to be used as the Baseline assessment)
  - Cogstate One Back (Section 6.2.9.1)
  - Cogstate Identification Test (Section 6.2.9.2)
  - Cogstate Detection Test (Section 6.2.9.3)

Eligible patients will be dispensed an electronic study drug dosing diary and study drug bottles containing open-label pitolisant (Section 5.2.1); patients will be instructed to take open-label pitolisant once daily in the morning upon wakening and to record in their dosing diary daily the date, exact time, and number of tablets taken (Section 5.4.1 and Appendix B).

Patients will be instructed to take their first dose of open-label pitolisant on the day after Visit 2 (first day of open-label pitolisant dosing is on Day 1).

Patients will be instructed to bring their electronic provisioned handheld device with their study drug dosing diary and all used and unused bottles of pitolisant with them to all on-site study visits. The study drug dosing diary will be completed for the entire study.

7.3. Open-Label Phase (Day 1 to Day 56)

All patients will receive treatment with open-label pitolisant in the Open-Label Phase of the study.

7.3.1. Dose Optimization Period (6 Weeks; Day 1 to Day 42)

Section 3.1.3.1 provides details on pitolisant dosing in the Dose Optimization Period

7.3.1.1. Telephone Contacts: TC 1 and TC 2 (Day 8 and Day 15 ±2 days)

Patients will be contacted by the study site by telephone on Day 8 and Day 15 (±2 days; TC 1 and TC 2, respectively) to assess for AEs and concomitant medication use, complete the ESS using their electronic provisioned handheld device, and review/confirm pitolisant titration and compliance. The C-SSRS, Since Last Visit will be completed by trained site staff using an electronic device (i.e., computer tablet) provided to each site.

7.3.1.2. Visit 3 (Day 22 ±2 Days)

The following assessments will be completed at Visit 3:

- Urine pregnancy test (FCBP only)
- Abbreviated physical examination (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Review of AEs
- Review of concomitant medications
- Review study drug compliance/accountability (Section 5.5/Section 5.6)
- C-SSRS, Since Last Visit (Appendix N)
- ESS (Section 6.2.1)
- CGI-S (Section 6.2.5)

Patients will be dispensed pitolisant in a quantity sufficient for 5 weeks of once daily administration (i.e., weeks 4, 5, 6 of the Dose Optimization Period and weeks 7 and 8 of the Stable Dose Period).

7.3.1.3. Telephone Contacts: TC 3 and TC 4 (Day 29 and Day 36 ±2 Days)

Patients will be contacted by the study site by telephone on Day 29 and Day 36 (±2 days; TC 3 and TC 4, respectively) to assess for AEs and concomitant medication use, complete the ESS using their electronic provisioned handheld device, and review/confirm study drug compliance. The C-SSRS, Since Last Visit will be completed by trained site staff using an electronic device (i.e., computer tablet) provided to each site.

7.3.2. Stable Dose Period (2 Weeks; Day 43 to Day 56)

Section 3.1.3.2 provides details on pitolisant dosing in the Stable Dose Period.

7.3.2.1. Telephone Contacts: TC 5 and TC 6 (Day 43 and Day 50 ±2 Days)

Patients will be contacted by the study site by telephone on Day 43 and Day 50 (±2 days; TC 5 and TC 6, respectively) to assess for AEs and concomitant medication use, complete the ESS using their electronic provisioned handheld device, and review/confirm study drug compliance. The C-SSRS, Since Last Visit will be completed by trained site staff using an electronic device (i.e., computer tablet) provided to each site.

On Day 43 (TC 5) and Day 50 (TC 6), patients will be reminded to record sleep diary data in their electronic provisioned handheld device for approximately 7 days prior to their next clinic visit (Visit 4).

On Day 50 (TC 6), patients will be reminded to record in their dosing diary using their electronic provisioned handheld device the date, exact time, and dose on the morning of their Week 8 visit (Visit 4).

7.3.2.2. End of Stable Dose Period: Visit 4 (Day 56 ±3 Days)

Visit 4 (Day 56 ±3 days; end of Stable Dose Period) is the last day of the Stable Dose Period and the last day of treatment with open-label pitolisant. Visit 4 should be performed at the same time of day as the Baseline visit (Visit 2). Except where indicated, all patients will complete all of the scheduled assessments.

The following assessments will be completed at Visit 4:

- Review of eligibility criteria [redacted]
- Urine pregnancy test (FCBP only)
- Urine drug screen (Table 6)
- Full physical examination (Section 6.3.2)
- Body weight
- Vital signs (Section 6.3.3)
- 12-lead ECG (Section 6.3.4)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 6)
- Blood sample for PK and CYP2D6 genotype assessments, at the same time as the clinical laboratory tests

- C-SSRS, Since Last Visit (Appendix N)
- Review of AEs
- Review of concomitant medications
- Review study drug compliance/accountability (Section 5.5/Section 5.6)
- ESS (Section 6.2.1)
- PGI-S (Section 6.2.3)
- PGI-C (EDS) (Section 6.2.10)
- IHSS (Section 6.2.2)
- CGI-S (Section 6.2.5)
- FOSQ-10 (Section 6.2.6)
- PROMIS-SRI (Section 6.2.7)
- SIQ (Section 6.2.8)
- Cogstate One Back Test (Section 6.2.9.1)
- Cogstate Identification Test (Section 6.2.9.2)
- Cogstate Detection Test (Section 6.2.9.3)

The results of the ESS at Visit 4 will be used to confirm patient eligibility for the Double-Blind Randomized Withdrawal Phase. [redacted]

Patients who are not eligible to be randomized in the Double-Blind Randomization Withdrawal Phase (i.e., non-responders) will be discontinued from study treatment and will receive Safety Follow-up TCs from the study site at 15 (±3) days and 30 (+3) days after their final dose of open-label pitolisant (Section 7.6).

7.4. Double-Blind Randomized Withdrawal Phase (Day 57 to Day 84)

Section 3.1.4 provides details on study drug dosing during the Double-Blind Randomized Withdrawal Phase.

7.4.1. Telephone Contact: TC 7 (Day 71 ±3 Days)

Patients will be contacted by the study site by telephone on Day 71 (±3 days; TC 7). The ESS, PGI-S, IHSS, PGI-C (IH), FOSQ-10, PROMIS-SRI, and SIQ will be patient administered using their electronic provisioned handheld device. The CGI-S and C-SSRS, Since Last Visit will be completed by trained site staff using an electronic device (i.e., computer tablet) provided to each site. The following assessments will be completed at TC 7:

- Review of AEs
- Review of concomitant medications
- Review study drug compliance/accountability (Section 5.5/Section 5.6)
- C-SSRS, Since Last Visit (Appendix N)
- ESS (Section 6.2.1)
- PGI-S (Section 6.2.3)
- IHSS (Section 6.2.2)
- PGI-C (IH) (Section 6.2.4)
- CGI-S (Section 6.2.5)
- FOSQ-10 (Section 6.2.6)
- PROMIS-SRI (Section 6.2.7)
- SIQ (Section 6.2.8)
- Patients will be reminded to record in their dosing diary using their electronic provisioned handheld device the date, exact time, and dose on the morning of their Week 12 visit (Visit 5).

7.4.2. End of Treatment: Visit 5 (Day 84 ±3 Days)

Visit 5 (Day 84 ±3 days) is the EOT Visit in the Double-Blind Randomized Withdrawal Phase. Visit 5 should be performed at the same time of day as Visit 4.

The assessments to be completed at the EOT Visit are the same as those listed for Visit 4 (end of Stable Dose Period; Section 7.3.2.2), with the addition of the PGI-C (IH) and Patient Cognitive and Meaningful Change interview, and the exceptions of the review of eligibility criteria and PGI-C (EDS). The Patient Cognitive and Meaningful Change interview will be conducted after completion of the safety and efficacy assessments and/or procedures.

Patients who complete the Double-Blind Randomized Withdrawal Phase of the study will receive two Safety Follow-up TCs from the study site, one at 15 (±3) days and the second at 30 (+3) days after the final dose of blinded study drug (Section 7.6); patients will also have the opportunity to enroll in a long-term, open-label safety study under a separate protocol. Patients who complete the Double-Blind Randomized Withdrawal Phase of the study and enroll directly in the long-term, open-label safety study are not required to complete the Safety Follow-up TCs.

7.5. Early Termination Visit

Every effort should be made to perform the ET Visit evaluations for patients who prematurely discontinue study drug in the Open-Label Phase or Double-Blind Randomized Withdrawal Phase of the study. At the ET Visit, the reason for early termination must be recorded.

The assessments to be performed at the ET Visit are the same as those listed for Visit 5 (End of Treatment [end of Double-Blind Randomized Withdrawal Phase]; Section 7.4.2).

7.6. Safety Follow-Up Telephone Contacts

Patients (responders, non-responders, and patients who prematurely discontinue study treatment) will receive a Safety Follow-up TC from the study site at 15 (±3) days and 30 (+3) days after their final dose of study treatment to assess for AEs and concomitant medication use.

Patients who complete the Double-Blind Randomized Withdrawal Phase of the study and enroll directly in the long-term, open-label safety study (under a separate protocol) are not required to complete the Safety Follow-up TCs.

An on-site unscheduled study visit (Section 7.7) will be requested if clinically indicated in the opinion of the Investigator at either of the two Safety Follow-up TCs.

7.7. Unscheduled Visits and Assessments

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.

At a minimum, the following assessments are to be performed at any unscheduled visit, whether conducted by telephone or on-site:

- Review of AEs
- Review of concomitant medications
- Review of study drug compliance/accountability (Section 5.5/Section 5.6)

Other assessments (e.g., vital signs, abbreviated physical examination, 12-lead ECGs; clinical laboratory tests; urine pregnancy test; C-SSRS, Since Last Visit) may be completed based on the reason for the unscheduled visit 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 their 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 their 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 makes 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 provides written informed consent through 30 days (+3 days) after final dose of study drug (Safety Follow-up TCs, Section 7.6).

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 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, he/she must notify the Sponsor **within 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 **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 e-mail, 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 e-mail capacity, a copy of the SAE report form may be sent to the Sponsor by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the time frames outlined.

If the Investigator does not have all the 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 by completing an Unanticipated Problem Form and e-mailing it to 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 patient and child.

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

9. STATISTICS

9.1. General Considerations

All safety and efficacy data will be listed and summarized.

Unless otherwise specified, Baseline for the study is Visit 2 and is defined as the last observed measurement, whether scheduled or unscheduled, prior to open-label study drug administration.

Safety and efficacy endpoints will be summarized by treatment group. In general, continuous variables will be summarized using the number of patients with data (n), mean, 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 SAP and 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 the CSR.

All values summarized will also be presented in listings.

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



[redacted]

9.1.3. Missing Data

Every effort will be made to retain patients in the study; however, patients are free to withdraw from the study at any time for any reason. Patients who withdrawal early will be asked to return to the clinic for an ET visit for completion of assessments (SOA). In the case of dropouts and missing data, a multiple imputation (MI) approach will be utilized. All patients with missing Week 12 data in the ITT population will be assigned values imputed via an MI approach, based on the reason for dropout:

Reason for Drop Out:	**Grouping:**
Adverse event (AE)	Group 2
Lack of effect (LOE)	Group 2
Patient decision	Group 1
Lost to follow-up	Group 1
No longer meets eligibility criteria	Group 1
Non-compliance with study protocol	Group 1
Non-compliance with study treatment	Group 1
Withdrawal of consent	Group 1
Patient replacement	Group 1
Other	Group 1

[redacted]

[redacted]

A similar imputation approach will be utilized for each of the continuous key secondary endpoints; full details will be provided in the SAP, including the random seeds to be used in the

above processes. Key secondary endpoints that are responder analyses will consider those with missing data to be non-responders.

9.2. Determination of Sample Size

The sample size in the Double-Blind Randomized Withdrawal Phase of the study is 128 patients randomized in a 1:1 ratio to one of two treatment groups (optimal dose of pitolisant [17.8 mg or 35.6 mg] or matching placebo). These estimates are based on the feasibility of enrollment and the goal of achieving statistically significant results for the effect of pitolisant on the symptom of EDS in patients with IH. The sample size is powered to show statistical significance.

The primary endpoint will be the mean change in ESS score from the end of the Stable Dose Period (Week 8) to the end of the Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo. [redacted]

Approximately 200 patients are planned for enrollment in the Open-Label Phase to achieve approximately 128 responder patients to be entered into the Double-Blind Randomized Withdrawal Phase of the study.

[redacted]

9.3. Analysis Populations

9.3.1. ITT Population

The ITT population will include all randomized patients who received at least one dose of study drug after the date of randomization. This population will be used to summarize the primary and other efficacy data. Patients will be analyzed according to their randomized treatment assignment.

9.3.2. Safety Population

The safety population will include all patients who are enrolled and take at least one dose of study drug. Patients will be analyzed according to treatment received. In the case of mis-dosing, patients will be counted in the active group if they receive any doses of active treatment and in the placebo group if they receive no active doses.

9.3.3. Pharmacokinetic Population

The PK population will include all patients who received at least one dose of pitolisant and who had at least one quantifiable serum concentration with appropriate dosing information (e.g., time of dosing).

9.3.4. Exposure-Response Population

The Exposure-Response population includes all patients who received at least one dose of study drug and who also have a baseline ESS score and at least one ESS score at Week 8 and/or Week 12.

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, number of patients enrolled, number and percentage of patients completing the study, and number and percentage of patients discontinuing from the study (including reasons for discontinuation) will be summarized. For Open-Label Phase items, percentages will be calculated using the number of patients enrolled as the denominator. For Double-Blind Randomized Withdrawal Phase items, percentages will be calculated using the number of patients entering the Double-Blind Randomized Withdrawal Phase as the denominator. Percentages for reasons for discontinuation will be calculated using the number of patients who discontinued.

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

9.4.2. Efficacy Analyses

Patients will undergo efficacy assessments at Screening (Visit 1; ESS and PGI-S only), Baseline (Visit 2, Day-1; all efficacy assessments except for PGI-C [IH]), Visit 3 (Day 22; ESS and CGI-S only), end of the Stable Dose Period (Visit 4, Day 56; all efficacy assessments except for PGI-C [IH]), TC 7 (all efficacy assessments except for the Cogstate Computerized Cognitive Test battery), and at the end of the Double-Blind Randomized Withdrawal Phase (Visit 5, Day 84; EOT Visit; all efficacy assessments). Additionally, the ESS will be administered at all TCs during the study.

9.4.2.1. Primary Efficacy Analysis

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the end of the Stable Dose Period to the end of the Double-Blind Randomized Withdrawal Phase for the active treatment group and the placebo group. The change from end of the Stable Dose Period (Visit 4) will be analyzed in an analysis of covariance (ANCOVA) model run on each of the 20 MI replicates and combined using SAS Procedure MIanalyze (Rubin 1976). Fixed effects will be included for treatment and end of the Stable Dose Period value. Least square means (LSMs), standard errors, and the LSM differences will be reported.

[redacted]

[redacted]

9.4.2.2. Secondary Efficacy Analysis

Analyses of the key, alpha-controlled, continuous secondary efficacy endpoints will utilize an approach identical to the one provided for the primary efficacy [redacted]. For responder analyses, the number and percentage of responders for each treatment group will be reported. [redacted]

9.4.3. Safety Analyses

All safety analyses will be completed for the safety population. All safety data will be tabulated and listed. No formal statistics will be performed for the safety analysis.

Safety will be assessed by monitoring and recording of all AEs from signing of the ICF through the final safety follow-up TC at 30 (+3) days after the final dose of study drug for both the Open-Label Phase (patients who are non-responders) and the Double-Blind Randomized Withdrawal Phase.

Adverse events that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class (SOC) and Preferred Term (PT). Incidence of TEAEs and SAEs will be summarized. Adverse events leading to study withdrawal, if any, will be listed separately. Adverse events will be summarized with counts and percentages.

Laboratory parameters will be summarized. 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 in and out of the normal range as well as by visit. Laboratory parameters will also be summarized by visit. The change from Baseline to each visit for vital sign variables will be summarized. 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 >450 msec for male patients and >470 msec for female patients, as well as QTcF >500 msec regardless of gender.

Results of the C-SSRS will be listed.

[redacted]

n_2 = the total planned sample size (128 patients),

[redacted]

9.4.5. Pharmacokinetic Analyses

Serum concentrations of pitolisant and BP1.3484 will be listed by week (i.e., Week 8 and Week 12) and summarized by specific intervals after dosing (0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, >24 h after the last dose).

Concentrations of pitolisant may be combined with data from other studies using the same bioanalytical method to describe the population PK parameters of pitolisant. The methodology will be reported in a separate analysis plan and the results will be reported in a separate population PK report.

Exploratory plots may be produced to evaluate whether there is a relationship between exposure to pitolisant (predicted C_{max}, AUC_{tau}, C_{trough}) and response based on the ESS. If an exposure-response relationship is evident from plots, an exposure-response model may be developed and reported in the population PK report.

10. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control systems will be implemented and maintained by the Sponsor and its designee(s) with SOPs, 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/Ethics Committee Approval

The Investigator or the Sponsor is responsible for submitting the following documents to the IRBs/ECs for review and, if applicable, approval: study protocol, ICF, 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 ICF 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 Process

All references to “patient” in this section refer to the study patient or their legally authorized representative.

The Sponsor (or its designee) will provide Investigators with an ICF for this study. Investigators may adapt the information to suit the needs of their institution, if necessary, but it must reflect the required elements of informed consent specified in 21 CFR Part 50.25. The final ICF must be accepted by the Sponsor and approved by the IRB/EC. Investigators must provide the Sponsor with an unsigned copy of the final ICF 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 ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each patient must sign and date an IRB/EC approved ICF written in language the patient can understand. The ICF should be as nontechnical

as practical and understandable to the patient. The ICF 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 ICF details the requirements of the participant and the fact that they are free to withdraw at any time without giving a reason and without prejudice to their further medical care. Before informed consent 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 ICF will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the patient's case history. All patients will receive a copy of their signed and dated ICF.

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

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 identification 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 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 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, e-mails, 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 documents, patient recruitment procedures, patients' compliance with the 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, ICFs, 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 are required to inform the Sponsor of all disclosable financial interests or arrangements (including those of their spouse and dependent children), prior to study initiation at the site, at study completion, and for 1 year following completion of the study in accordance with 21 CFR Part 54. In addition, the Investigator or Sub-Investigators must promptly notify the Sponsor if there are any reportable changes that occur during this period.

Disclosable financial interests or arrangements, or the absence thereof, will be recorded on the Financial Disclosure for Clinical Investigators Form at study initiation and at study completion.

Any Investigator(s) added as investigational staff to the Form FDA 1572 must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the study. Any Investigator(s) leaving the study prior to completion will also complete their Financial Disclosure for Clinical Investigators Form at that time.

12.4. Suspension or Termination of the Study or Investigational Site

12.4.1. Suspension of the 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 the 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 CSR is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required. Where required by applicable regulations, an Investigator signatory will be identified for the approval of the CSR. 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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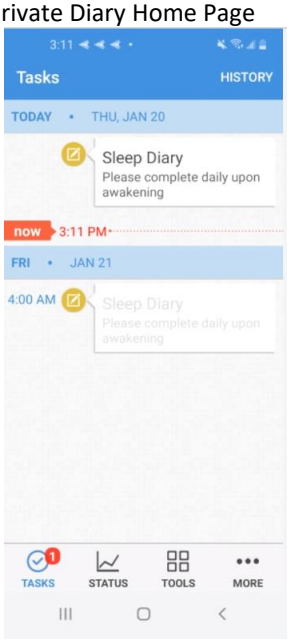
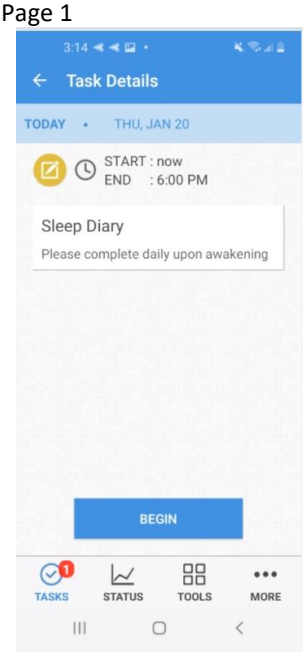
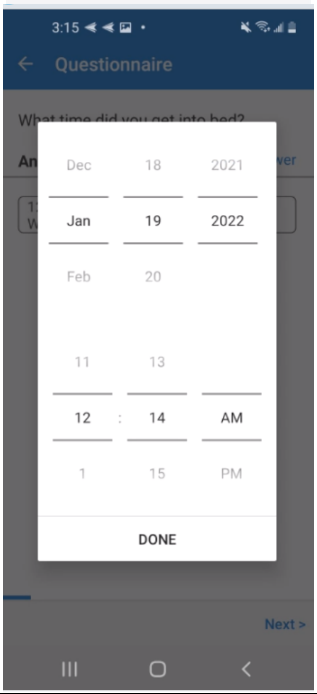
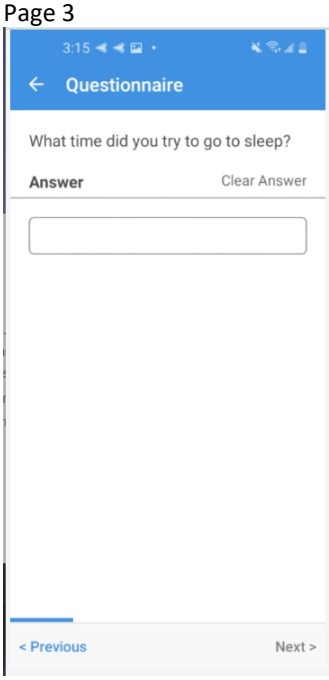
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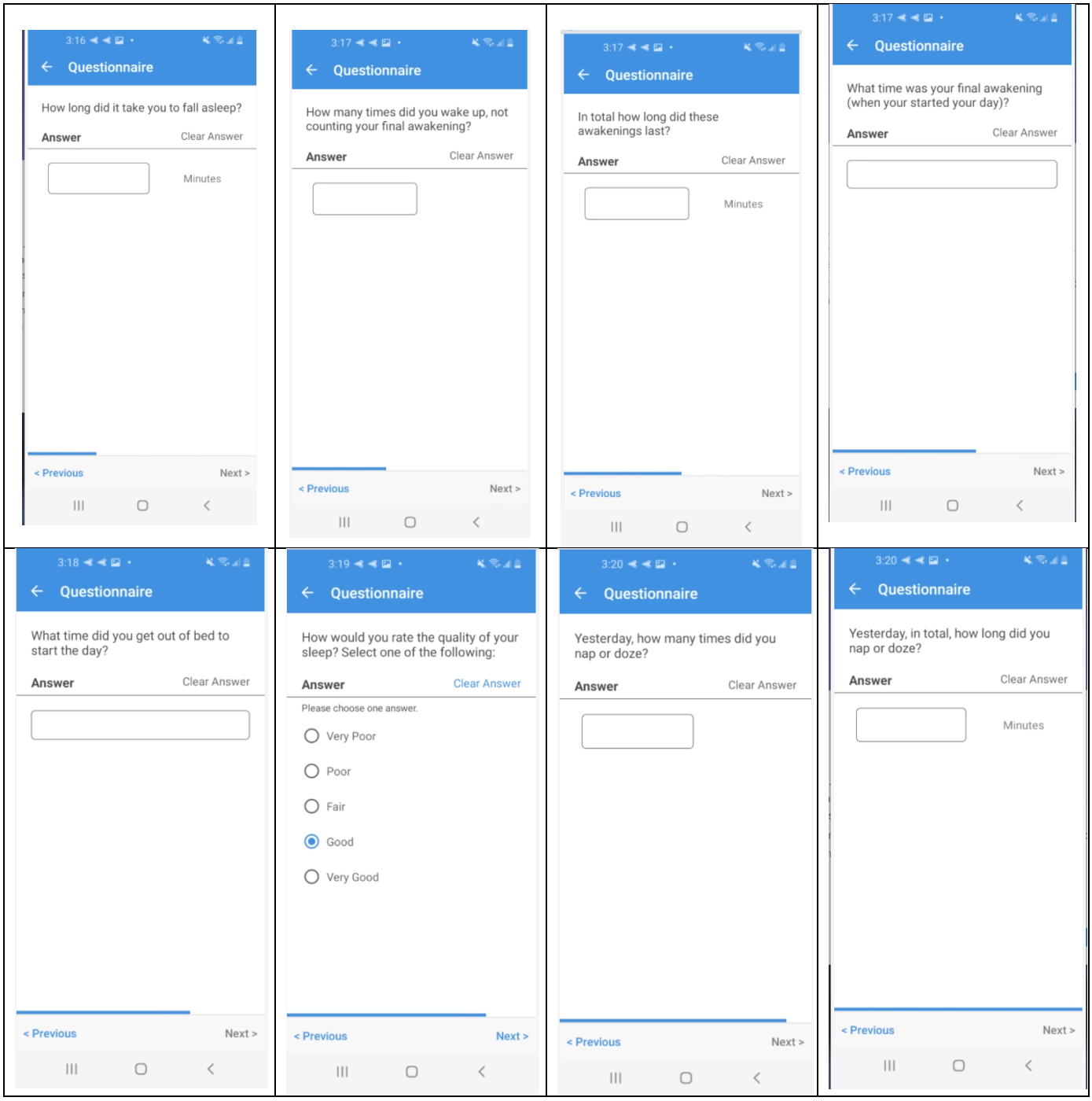
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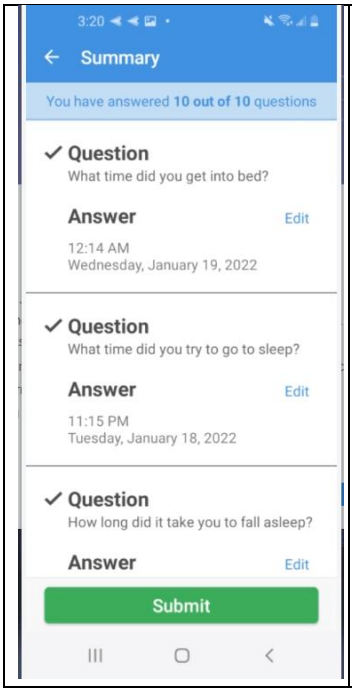
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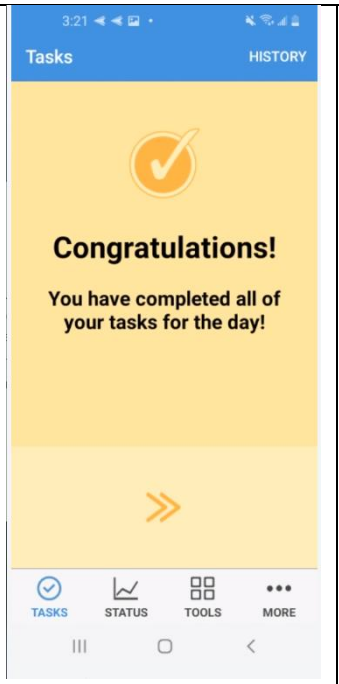
APPENDIX A. PATIENT SLEEP DIARY FOR SCREENING (EXAMPLE)

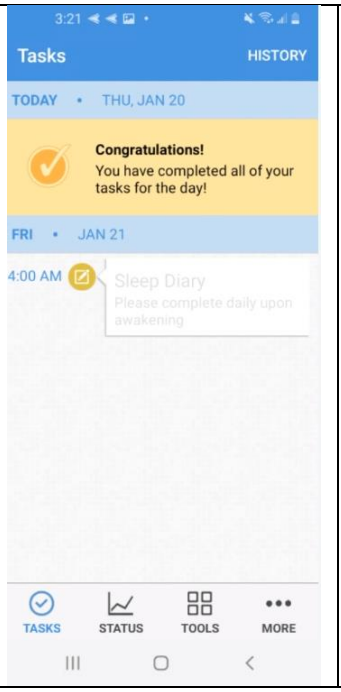
Sleep Diary

Private Diary Home Page	Page 1	Page 2	Page 3
		 	


Questionnaire
How long did it take you to fall asleep?
Answer
Clear Answer
Minutes
< Previous
Next >
Questionnaire
How many times did you wake up, not counting your final awakening?
Answer
Clear Answer
< Previous
Next >
Questionnaire
In total how long did these awakenings last?
Answer
Clear Answer
Minutes
< Previous
Next >
Questionnaire
What time was your final awakening (when your started your day)?
Answer
Clear Answer
< Previous
Next >
Questionnaire
What time did you get out of bed to start the day?
Answer
Clear Answer
< Previous
Next >
Questionnaire
How would you rate the quality of your sleep? Select one of the following:
Answer
Clear Answer
Please choose one answer.
Very Poor
Poor
Fair
Good
Very Good
< Previous
Next >
Questionnaire
Yesterday, how many times did you nap or doze?
Answer
Clear Answer
< Previous
Next >
Questionnaire
Yesterday, in total, how long did you nap or doze?
Answer
Clear Answer
Minutes
< Previous
Next >

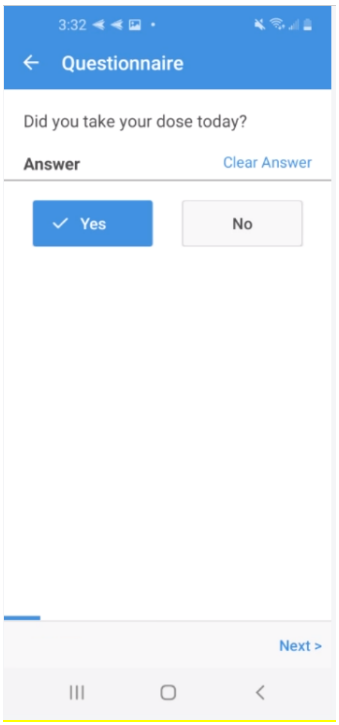

3:20
Summary
You have answered 10 out of 10 questions
Question
What time did you get into bed?
Answer
Edit
12:14 AM
Wednesday, January 19, 2022
Question
What time did you try to go to sleep?
Answer
Edit
11:15 PM
Tuesday, January 18, 2022
Question
How long did it take you to fall asleep?
Answer
Edit
Submit


3:21
Tasks
HISTORY
Congratulations!
You have completed all of your tasks for the day!
TASKS
STATUS
TOOLS
MORE

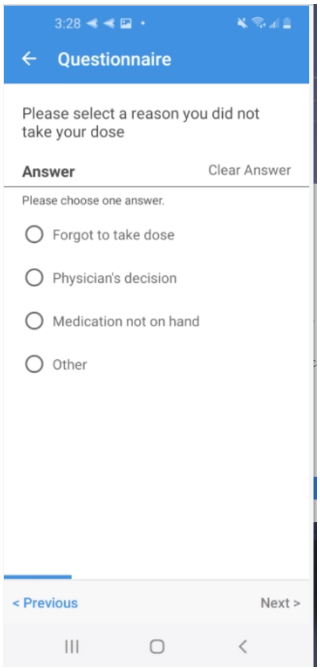

3:21
Tasks
HISTORY
TODAY • THU, JAN 20
Congratulations!
You have completed all of your tasks for the day!
FRI • JAN 21
4:00 AM
Sleep Diary
Please complete daily upon awakening
TASKS
STATUS
TOOLS
MORE

APPENDIX B. PATIENT STUDY DRUG DOSING DIARY (EXAMPLE)

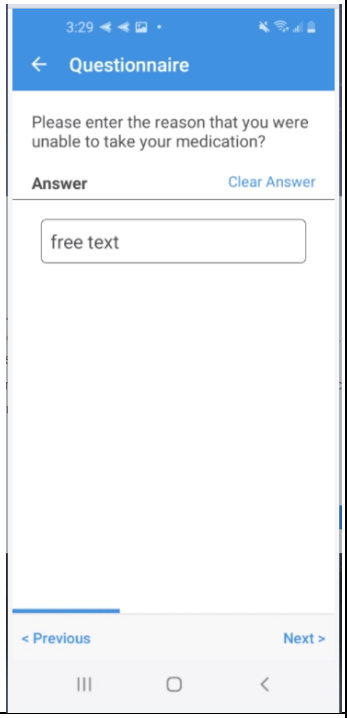
Dosing Diary Randomized

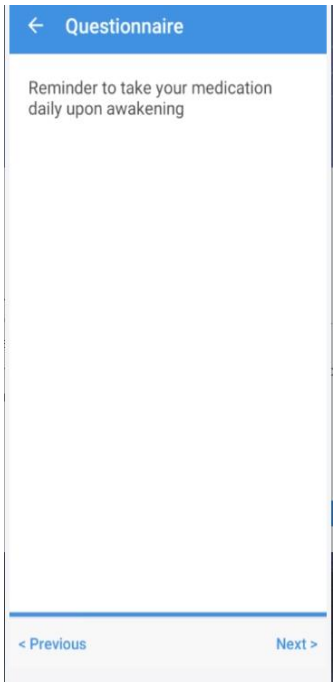


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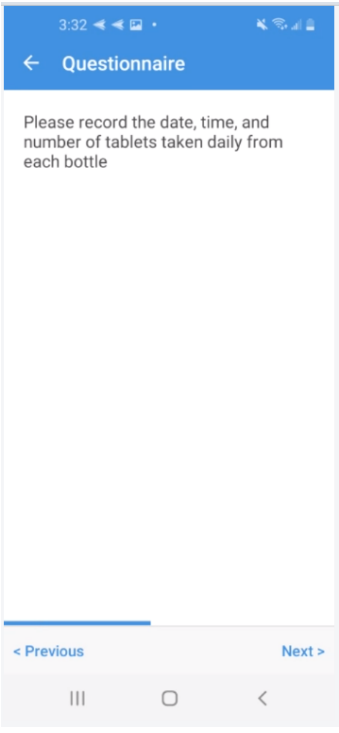


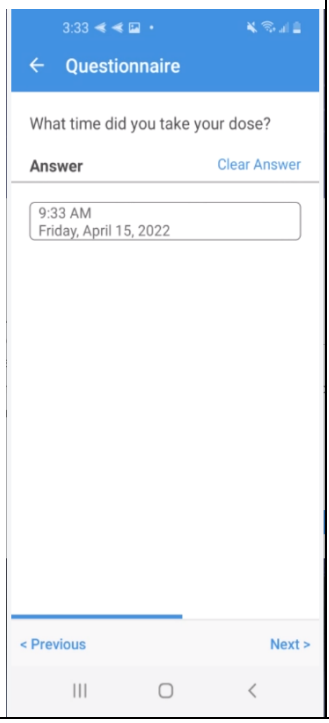
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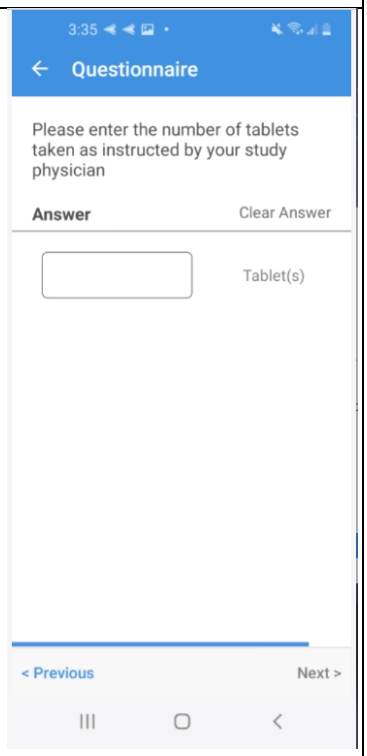


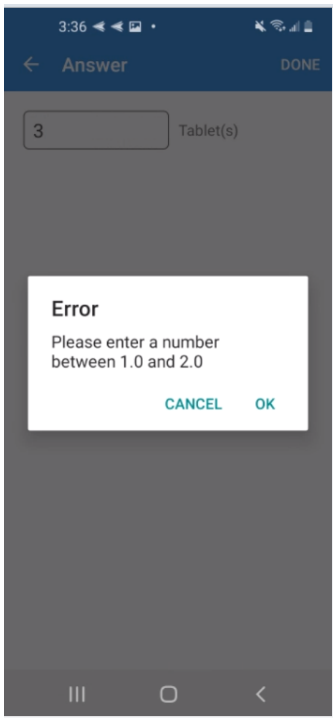
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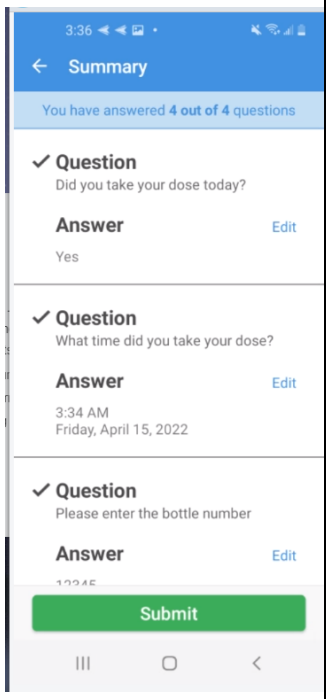


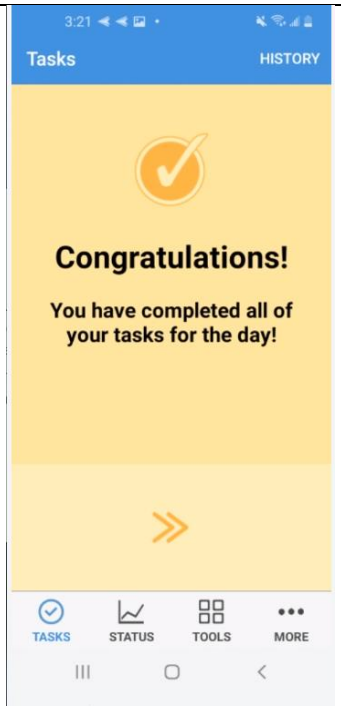




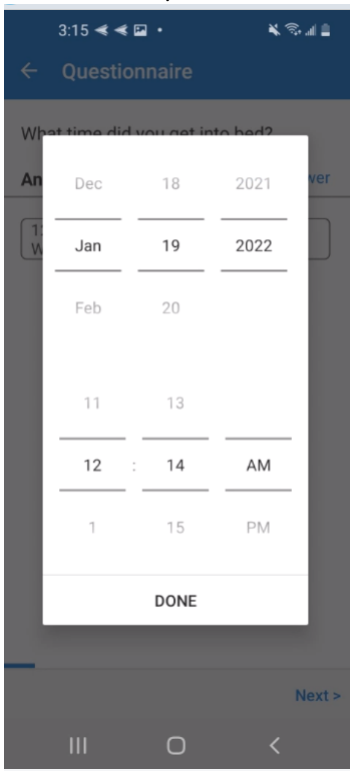




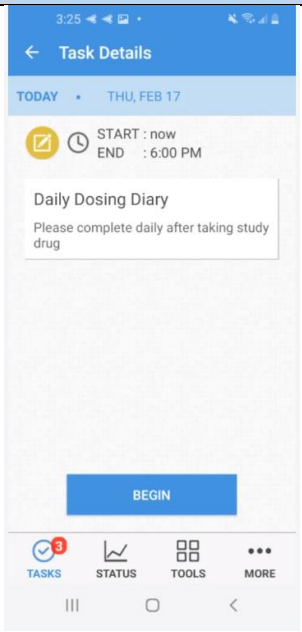
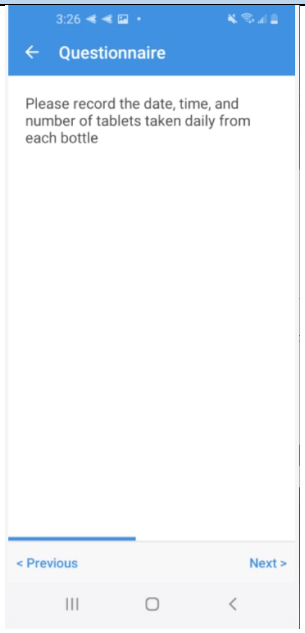
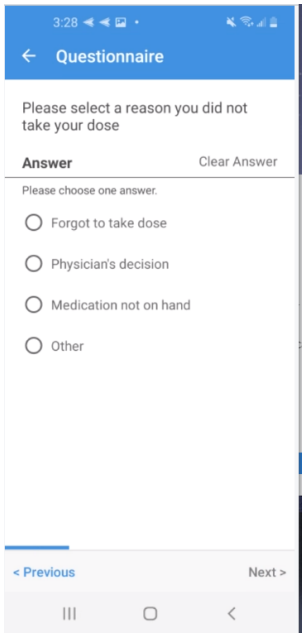




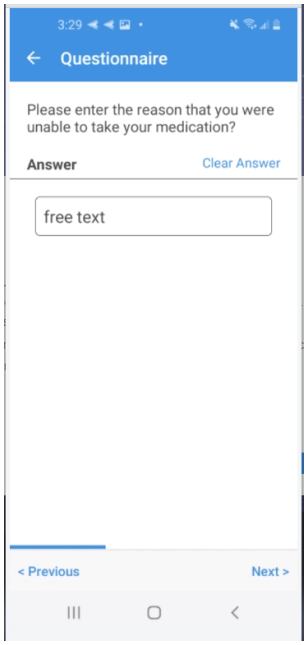
Select time/date screen



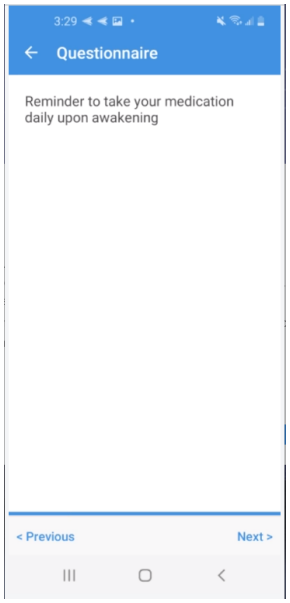
Dosing Diary Titration

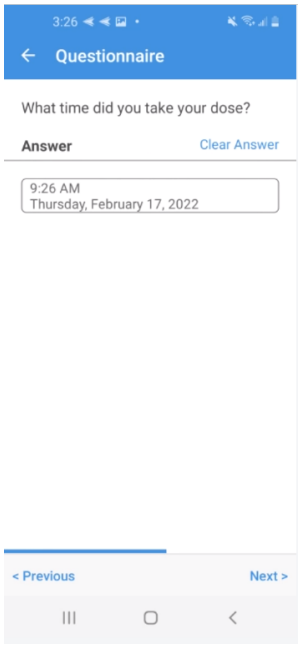
			Task Display
		 If selected "yes"	If "No" was selected 

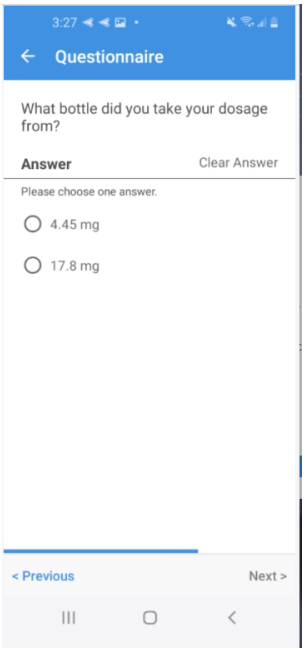
If “other” was selected



Screen after entering reason for not take dose.



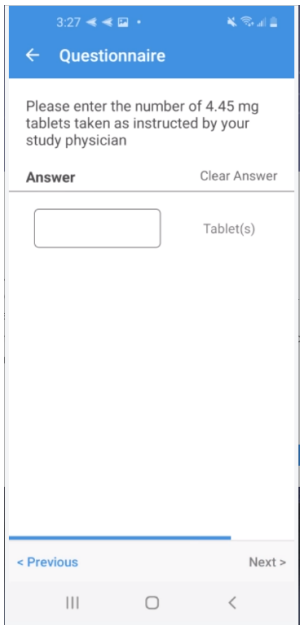




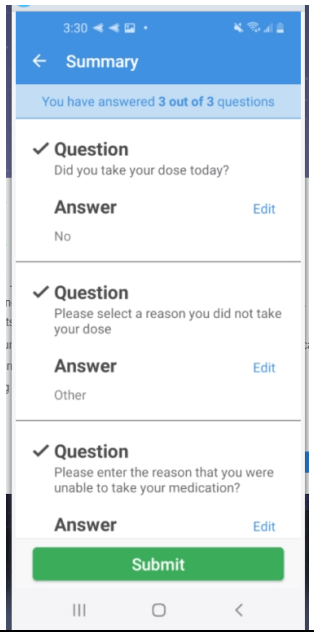
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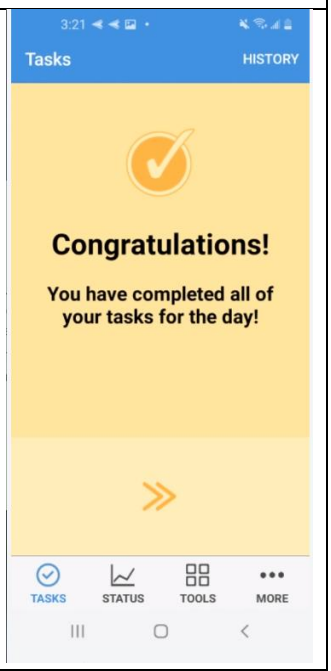


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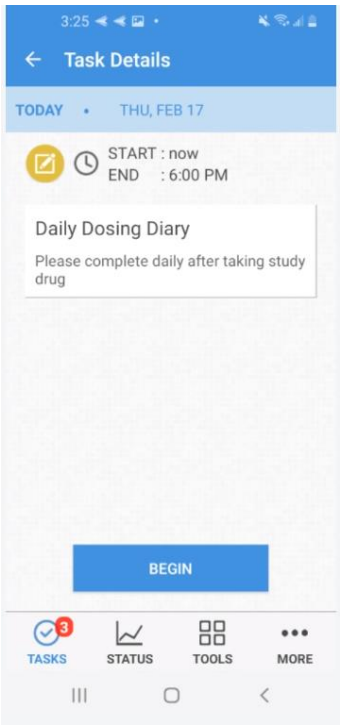


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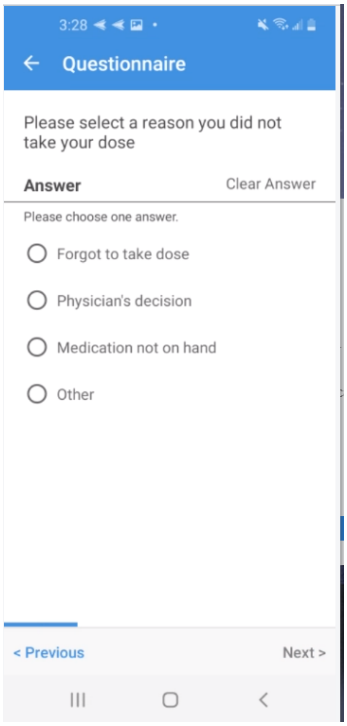


Dosing Diary V2

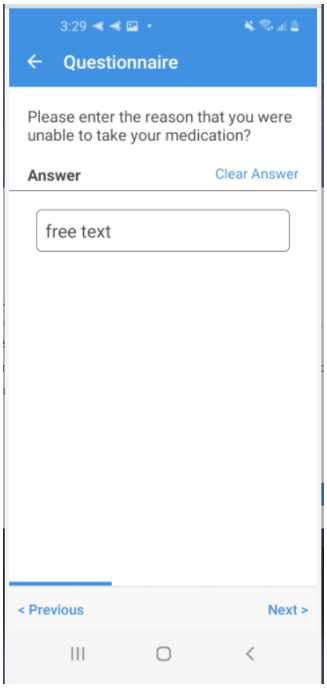


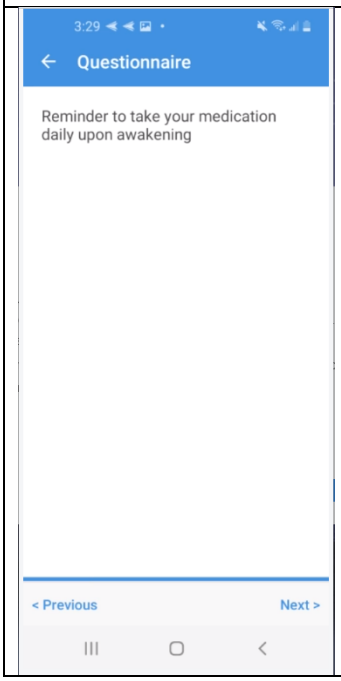


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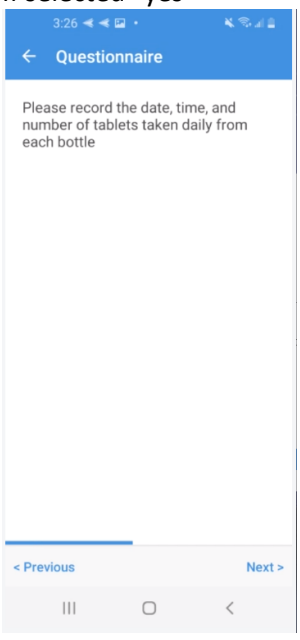


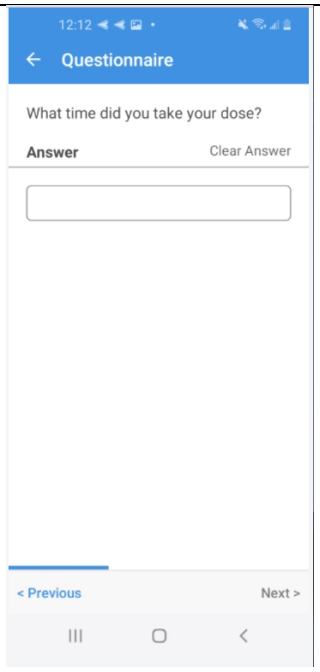
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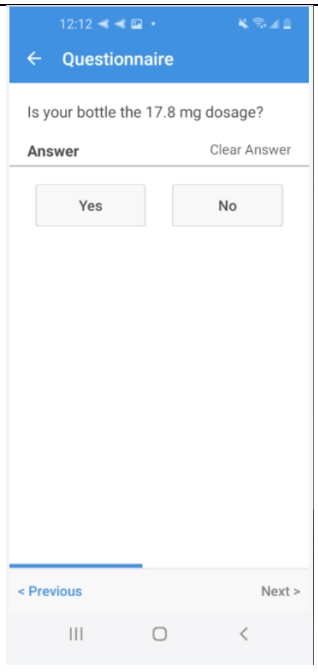




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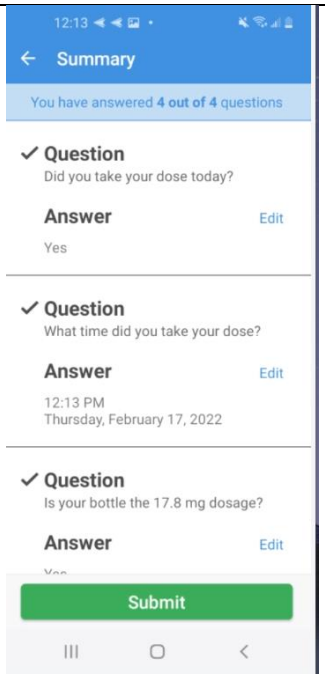


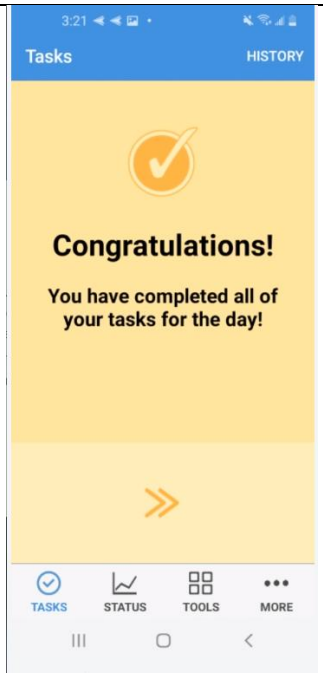
If selected “No”



If selected “yes”







APPENDIX C. EXAMPLES OF STRONG CYP2D6 INHIBITORS, STRONG CYP3A4 INDUCERS, CENTRALLY ACTING H1R ANTAGONISTS, AND MEDICATIONS THAT PROLONG QT INTERVAL

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_1R antagonists	pheniramine maleate, diphenhydramine, promethazine (antihistamines), imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)

CYP = cytochrome P450; H_1R = histamine 1 receptor.

APPENDIX D. EPWORTH SLEEPINESS SCALE (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life in the past week.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading _____	___
Watching TV _____	___
Sitting inactive in a public place (e.g., a theater or a meeting) _____	___
As a passenger in a car for an hour without a break _____	___
Lying down to rest in the afternoon when circumstances permit _____	___
Sitting and talking to someone _____	___
Sitting quietly after a lunch without alcohol _____	___
In a car or bus, while stopped for a few minutes in traffic _____	___

THANK YOU FOR YOUR COOPERATION

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APPENDIX E. IDIOPATHIC HYPERSOMNIA SEVERITY SCALE (IHSS)

IDIOPATHIC HYPERSOMNIA SEVERITY SCALE (IHSS)

Taking into account your symptoms over the past 7 days.

1. What is for you the ideal duration of your nighttime sleep *(e.g., during the weekend or on vacation)*?

3 ❒ 11 hours or more
2 ❒ more than 9 hours and less than 11 hours
1 ❒ between 7 and 9 hours
0 ❒ less than 7 hours

2. When circumstances require you to wake up at a certain time in the morning *(e.g., for work or study, or to take your children to school during the week),* do you feel like you have not had enough sleep?

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

3. Is it extremely difficult for you, or even impossible, to wake up in the morning without multiple alarms ("*alarm reminders")* or help from a family member?

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

4. After a night's sleep, how long does it take you to feel operational after getting up *(i.e., in full physical and mental control)*?

4 ❒ 2 hours or more
3 ❒ more than 1 hour but less than 2 hours
2 ❒ between 30 minutes and 1 hour
1 ❒ less than 30 minutes
0 ❒ I feel operational as soon as I wake up

5. Within minutes of waking up, do you ever do and/or say things that are out of character, and/or make clumsy mistakes *(e.g., trip, break or drop things)*?

3 ❒ always 2 ❒ often 1 ❒ sometimes 0 ❒ never

6. During the day, when circumstances allow, do you ever take a nap?

4 ❑ very often (6-7 times per week)
3 ❑ often (4-5 times per week)
2 ❑ sometimes (2-3 times per week)
1 ❑ rarely (once per week)
0 ❑ never

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7. What is for you the ideal length of your naps *(e.g., during the weekend or on vacation)?*
   ☞ *Note: If you take multiple naps, add up the cumulative duration of the naps*

   3 ❒ 2 hours or more
   2 ❒ more than 1 hour and less than 2 hours
   1 ❒ less than 1 hour
   0 ❒ No nap

8. Typically, how do you feel after a nap?

   3 ❑ very sleepy 2 ❑ sleepy 1 ❑ alert 0 ❑ very alert

9. During daytime, during activities that are not very stimulating, do you ever struggle to stay awake?

   4 ❑ very often (at least twice a day)
   3 ❑ often (4-7 times per week)
   2 ❑ sometimes (2-3 times per week)
   1 ❑ rarely (once a week, or once a week but not every week)
   0 ❑ never

10. Do you believe that your hypersomnia has an impact on your general condition (*i.e., lack of energy, lack of motivation to do things, physical fatigue during exertion, reduced physical performance*)?

   4 ❒ very significantly 3 ❒ significantly 2 ❒ moderately 1 ❒ mildly 0 ❒ no impact

11. Do you believe that your hypersomnia interferes with your intellectual functioning *(i.e., concentration problems, memory problems, reduced mental performance)*?

   4 ❒ very significantly 3 ❒ significantly 2 ❒ moderately 1 ❒ mildly 0 ❒ no interference

12. Do you believe that your hypersomnia affects your mood *(e.g., sadness, anxiety, hypersensitivity, irritability)*?

   4 ❒ extremely 3 ❒ quite a lot 2 ❒ moderately 1 ❒ mildly 0 ❒ not at all

13. Do you believe that your hypersomnia prevents you from performing daily tasks properly *(family responsibilities, chores, leisure, professional activity)*?

   4 ❒ extremely 3 ❒ quite a lot 2 ❒ moderately 1 ❒ mildly 0 ❒ not at all

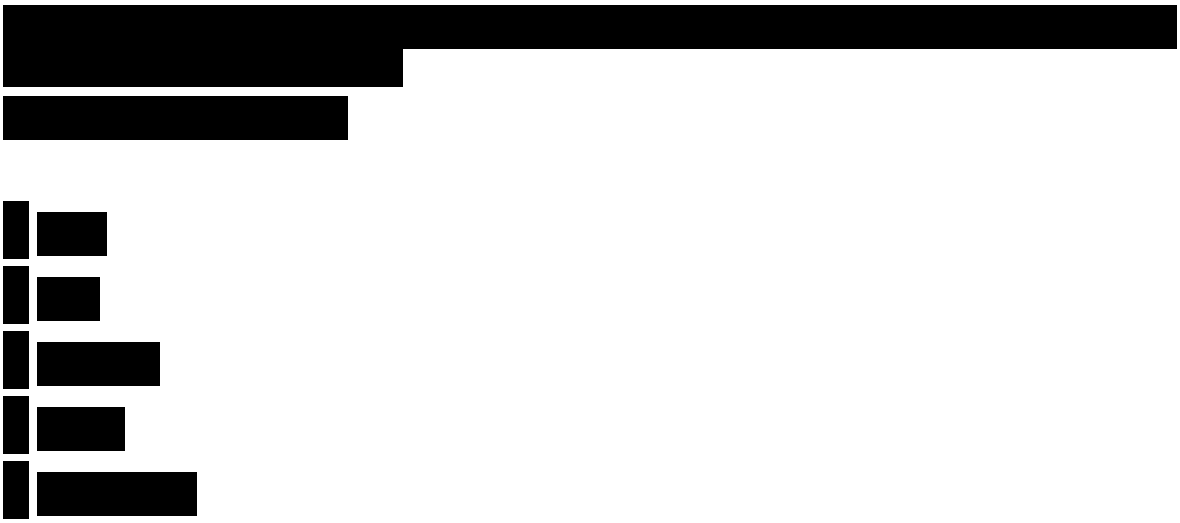
14. Do you believe that your hypersomnia interferes with driving a car?

   4 ❒ very significantly 3 ❒ significantly 2 ❒ moderately 1 ❒ mildly 0 ❒ no interference

   ❒ I don't drive

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APPENDIX F. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S) FOR EXCESSIVE DAYTIME SLEEPINESS (EDS)



APPENDIX G. PATIENT GLOBAL IMPRESSION OF CHANGE FOR SYMPTOMS OF IDIOPATHIC HYPERSOMNIA (PGI-C [IH])

[redacted]

APPENDIX H. CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGI-S) FOR IH

[redacted]

APPENDIX I. FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE 10-ITEM VERSION (FOSQ-10)

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put a (_) in the box for your answer to each question. Select only **one** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1. Do you have difficulty concentrating on the things you do because you are sleepy or tired?		❒	❒	❒	❒
2. Do you generally have difficulty remembering things, because you are sleepy or tired?		❒	❒	❒	❒
3. Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒
4. Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5. Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒

	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
6. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	❒	❒	❒	❒

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
7. Do you have difficulty watching a movie or videotape because you become sleepy or tired?	❒	❒	❒	❒	❒
8. Do you have difficulty being as active as you want to be in the <u>evening</u> because you are sleepy or tired?		❒	❒	❒	❒
9. Do you have difficulty being as active as you want to be in the <u>morning</u> because you are sleepy or tired?		❒	❒	❒	❒

	(0) I don't engage in sexual activity for other reasons	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
10. Has your desire for intimacy or sex been affected because you are sleepy or tired?	❒	❒	❒	❒	❒

Thank you for completing this questionnaire.

APPENDIX J. PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM SLEEP-RELATED IMPAIRMENT (PROMIS-SRI) – SHORT FORM 8A

Sleep-Related Impairment – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep10	I had a hard time getting things done because I was sleepy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep119	I felt alert when I woke up	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep18	I felt tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep25	I had problems during the day because of poor sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep27	I had a hard time concentrating because of poor sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep30	I felt irritable because of poor sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep6	I was sleepy during the daytime.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep7	I had trouble staying awake during the day.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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APPENDIX K. SLEEP INERTIA QUESTIONNAIRE (SIQ)

The Sleep Inertia Questionnaire (SIQ)

Please use the following scale to answer the questions below:

	1 = Not at all	**2 = A little**	**3 = Somewhat**	**4 = Often**	**5 = All the time**
On a **typical morning in the past week**, after you wake up, to what extent do you …					
1.	Have problems getting out of bed?	1	2	3	4	5
2.	Need an alarm to wake up?	1	2	3	4	5
3.	Hit the snooze button on the alarm?	1	2	3	4	5
4.	Bump into and drop things?	1	2	3	4	5
5.	Notice that you move more slowly?	1	2	3	4	5
6.	Notice that you feel sleepy?	1	2	3	4	5
7.	Notice your eyes feeling heavy, sore, or itchy?	1	2	3	4	5
8.	Notice your arms and/or legs feeling tired or heavy?	1	2	3	4	5
9.	Notice that your mind feels groggy, fuzzy or hazy?	1	2	3	4	5
10.	Notice that you get winded more easily?	1	2	3	4	5
11.	Notice that it is difficult to keep your balance?	1	2	3	4	5
12.	Notice that you feel tense?	1	2	3	4	5
13.	Feel anxious about the upcoming day?	1	2	3	4	5
14.	Dread starting your day?	1	2	3	4	5
15.	Wish you could sleep more?	1	2	3	4	5
16.	Have difficulty concentrating?	1	2	3	4	5
17.	Find that you think more slowly?	1	2	3	4	5
18.	Find that you think react more slowly?	1	2	3	4	5
19.	Find that you make more mistakes/errors?	1	2	3	4	5
20.	Can't imagine being able to wake up?	1	2	3	4	5
21.	Have difficulty getting your thoughts together?	1	2	3	4	5
22.	How long does it take you to 'come to' in the morning? _____ minutes.					
	22b. How many days per week is this the case? _____.					

APPENDIX L. PATIENT GLOBAL IMPRESSION OF CHANGE FOR EDS (PGI-C [EDS])

APPENDIX M. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), BASELINE/SCREENING

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

	Most Severe	Most Severe
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** <u>Past X Months</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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APPENDIX N. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), SINCE LAST VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it"*.
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*.
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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