Official Title of Study: An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients With Idiopathic Hypersomnia Who Completed Study HBS-101-CL-010

NCT Number: NCT05458128

Protocol Date (last revision date): August 28, 2023

CLINICAL STUDY PROTOCOL: HBS-101-CL-011

Protocol Title:	An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia who Completed Study HBS-101-CL-010
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:	[redacted]
Medical Project Leader:	
Operational Lead:	
Effective Date:	Amendment 2 28AUG2023

Confidentiality Statement
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SPONSOR SIGNATURE

Protocol Title: An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia who Completed Study HBS-101-CL-010

Protocol Number: HBS-101-CL-011

This protocol (Amendment 2) has been reviewed and approved by the Sponsor.



INVESTIGATOR'S AGREEMENT

TITLE: An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia who Completed Study HBS-101-CL-010

I have received and read the current Investigator's Brochure for pitolisant. I have read the HBS-101-CL-011 protocol (Amendment 2) 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: _____

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-011
PHASE OF DEVELOPMENT:	3

PROTOCOL TITLE: An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia who Completed Study HBS-101-CL-010

NUMBER OF PLANNED SUBJECTS:

Approximately [redacted] patients. The number of enrolled patients will depend on the final number of patients who completed the Double-Blind Randomized Withdrawal Phase of HBS-101-CL-010 and who agree to participate in the open-label study.

STUDY SITES: Approximately [redacted] sites in the United States (US)

STUDY OBJECTIVES:

Primary Objective

The primary objective of this study is to assess the long-term safety and effectiveness of pitolisant in patients with idiopathic hypersomnia (IH) who completed the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010.

METHODOLOGY:

This is a Phase 3 open-label, long-term study to evaluate the long-term safety and effectiveness of pitolisant in adult patients with IH. Patients who complete the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 (i.e., completed the End-of-Treatment [EOT] Visit/Visit 5 in the HBS-101-CL-010 study) and who meet the inclusion/exclusion criteria for study HBS-101-CL-011 are eligible for enrollment. Failure to comply with the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010, as determined by the Medical Monitor, will preclude patients from participating in the open-label, long-term study.

Patients who complete study HBS-101-CL-010 will have up to 7 days from the EOT Visit/Visit 5 to enroll in study HBS-101-CL-011 and begin open-label pitolisant. The EOT Visit/Visit 5 for study HBS-101-CL-010 is the Screening Visit for study HBS-101-CL-011. The results of assessments performed at this visit will be used to confirm eligibility for study HBS-101-CL-011.

The results of assessments performed at the EOT Visit/Visit 5 from study HBS-101-CL-010 will be used as Baseline values for this study.

Patients will provide written informed consent at the Screening Visit, or informed consent may be provided remotely for patients who do not immediately enroll in the long-term study (i.e., up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010). Enrolled patients will be dispensed open-label pitolisant and may be titrated up to a maximum once daily dose of 35.6 mg, based on the Investigator's assessment of safety/tolerability and effectiveness, during a 3-week Titration Period (Day 1 to Day 21) in accordance with the schedule:

- [redacted]

If a patient is identified as a cytochrome P450 (CYP) 2D6 poor metabolizer (PM) and had previously received pitolisant at a stable once daily dose of 35.6 mg, the Investigator should consult with the Medical Monitor prior to adjusting the daily pitolisant dose to 35.6 mg or deciding to allow the patient to remain at a once daily pitolisant dose of 35.6 mg. If a patient is identified as a CYP2D6 PM and had not previously received pitolisant at a stable once daily dose of 35.6 mg, the patient may only receive a maximum once daily dose of 17.8 mg.

Patients will take their first dose of pitolisant [redacted] mg) on Day 1, which is the morning after the Screening Visit (or up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 if a patient does not choose to immediately enroll in the open-label, long-term study). Patients may remain on a lower dose of pitolisant for longer than one week or switch between doses (higher or lower) based on Investigator assessment of safety/tolerability and effectiveness during the 3-week Titration Period. Patients will receive telephone contacts (TCs) from the site on Day 8 (TC 1) and Day 15 (TC 2) during the Titration Period to assess for adverse events (AEs) and concomitant medication use, complete the Columbia-Suicide Severity Rating Scale (C-SSRS), and review/confirm pitolisant dose titration.

The Long-Term Dosing Period will begin on Day 22 and will continue until the patient discontinues from the study or the Sponsor elects to terminate the study (i.e., End-of-Study [EOS]). Patients will complete an on-site study visit on Day 22 (Visit 2) during the Long-Term Dosing Period and will receive a TC from the site approximately 30 days later, on Day 52 (TC 3). TC visits will occur monthly in between each on-site visit. An on-site study visit will occur approximately 180 days after Visit 2 on Day 202 (Visit 3). On-site study visits will occur approximately every 6 months and TCs approximately every one month in between until the patient withdraws from the study or the study is terminated by the [redacted]

At all on-site study visits during the Long-Term Dosing Period, assessments for safety/tolerability and effectiveness will be performed. At all TCs during the Long-Term Dosing Period, AEs and concomitant medication use will be recorded, the C-SSRS will be completed, and the current dose of pitolisant and receipt of study drug shipments will be confirmed.

Pitolisant in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration will be provided to enrolled patients every 3 months (90 days) either via mail or at the on-site study visits; additional pitolisant may be dispensed between TCs and/or at on-site visits if necessary.

All patients will receive Safety Follow-Up TCs from the study site 15 days and 30 days after their final dose of pitolisant, to assess for AEs and concomitant medication use.

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 informed consent.
2. Completed the Double-Blind Randomized Withdrawal Phase (EOT/Visit 5) from the HBS-101-CL-010 study.
3. A patient who is a female of child-bearing potential must have a negative urine pregnancy test at the Screening Visit. A patient who is a female of child-bearing potential must 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.
4. Must have a negative result on urine drug screen at the Screening Visit, except for medications that are prescribed by a healthcare provider for medical conditions.

5. 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 the study:

1. Does not agree to discontinue any prohibited medication or substances listed in the protocol.
2. 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.
3. Participation in an interventional research study with an investigational medication or device, other than pitolisant, for the duration of the study.
4. 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).
5. Is receiving or is unable to discontinue a medication known to prolong the QT interval.
6. 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 or "yes" on any question in the suicidal behavior section of the C-SSRS, Since Last Visit.
7. 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.

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 (8.9 mg to 35.6 mg) once daily in the morning upon wakening.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

This is an open-label study; all patients will receive pitolisant.

DURATION OF TREATMENT:

The study may be multi-year in duration. The study will remain open until all patients discontinue from pitolisant or the Sponsor elects to terminate the study. All patients will be followed for safety until 30 days after their final dose of pitolisant.

STUDY ASSESSMENTS:

Safety Assessments:

Safety will be assessed by monitoring and recording of all AEs from the signing of the informed consent form (ICF) throughout the final Safety Follow-Up TC 30 days after the final dose of pitolisant. Suicide risk and suicidality will be assessed using the C-SSRS at every on-site study visit and TC during the study. Safety assessments also include physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and concomitant mediation use.

Effectiveness Assessments:

Effectiveness of pitolisant will be evaluated using the Epworth Sleepiness Scale (ESS), Idiopathic Hypersomnia Severity Scale (IHSS), Clinical Global Impression of Severity for IH (CGI-S [IH]),

Patient Global Impression of Severity for EDS (PGI-S [EDS]), 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). Patients will undergo effectiveness assessments at on-site visits.

STUDY ENDPOINTS:

Safety Endpoints:

The long-term safety and tolerability of pitolisant will be evaluated by the incidence of AEs and changes in clinical laboratory test results, vital signs, 12-lead ECGs, and C-SSRS assessment.

[redacted]

STATISTICAL METHODS:

General Conventions:

All analyses will be reported by the treatment received in the Double-Blind Withdrawal Phase of the HBS-101-CL-010 study (i.e., pitolisant or placebo) and overall.

- Demographics and baseline characteristics for patients who received at least one dose of open-label study drug in study HBS-101-CL-011 will be reported.
- Baseline safety and effectiveness data will be reported with Baseline defined as the EOT Visit/Visit 5 from study HBS-101-CL-010, which are the assessments prior to the first dose of open-label pitolisant.
- AE and concomitant medications started on or after the first dose of open-label pitolisant in study HBS-101-CL-011 will be reported with counts from, and percentages of, patients in the safety population.

Determination of Sample Size:

There is no pre-determined sample size; the sample size will be determined based upon the number of patients who complete study HBS-101-CL-010 and enroll into this protocol.

Analysis population:

All analyses will be performed on the Safety Population, which includes all patients receiving at least one dose of open-label pitolisant in this study.

Safety Analyses:

All safety analyses will be completed for the Safety Population. All safety data will be listed and summarized.

Effectiveness Analyses:

The effectiveness outcome measures will be measured at all on-site visits and include ESS, IHSS, CGI-S (IH), PGI-S (EDS), FOSQ-10, PROMIS-SRI, and SIQ.

SCHEDULE OF ASSESSMENTS (SOA)

	Screening Visit[a]	3-Week Titration Period[b] Day 1 to 21			Long-Term Dosing Period[c] Day 22 to EOS			EOT/ET[f] Visit (±7)	Safety F-Up[g] TC	Unsch Visits[h]
		Week 1	Week 2	Week 3	Week 4	Months 2, 3, and Monthly Between On-Site Visits	Months 7, 13 and Every 6 Months			
Visit/TC Study Day Window (days)	Visit 1[b] Day -1	Day 1[d]	TC 1 Day 8 (±7)	TC 2 Day 15 (±7)	VISIT 2 Day 22 (±7)	Telephone Contacts[e]: Day 52 (Month 2/TC 3), Day 82 (Month 3/TC 4), and Monthly Between On-Site Visits through EOS (±7)	On-Site Visits: Day 202 (Month 7/Visit 3), Day 382 (Month 13/Visit 4), and Every 6 Months through EOS (±7)			
Informed consent	X									
Assess/confirm eligibility	X									
Demographics	X									
Medical History	X									
Urine pregnancy test (FCBP)	X				X		X	X		
Urine drug screen (dipstick)[a]	X						X			
Full physical examination	X				X		X	X		
Body weight	X				X		X	X		
Clinical laboratory tests	X						X	X		
Vital signs[i]	X				X		X	X		
12-lead ECG[j]	X						X	X		
C-SSRS	X		X	X	X	X	X	X		
Dispense/confirm receipt of study drug[k]	X				X	X	X			

	Screening Visit[a]	3-Week Titration Period[b] Day 1 to 21			Long-Term Dosing Period[c] Day 22 to EOS			EOT/ET[f] Visit (±7)	Safety F-Up[g] TC	Unsch Visits[h]
		Week 1	Week 2	Week 3	Week 4	Months 2, 3, and Monthly Between On-Site Visits	Months 7, 13 and Every 6 Months			
Visit/TC Study Day Window (days)	Visit 1[b] Day -1	Day 1[d]	TC 1 Day 8 (±7)	TC 2 Day 15 (±7)	VISIT 2 Day 22 (±7)	Telephone Contacts[e]: Day 52 (Month 2/TC 3), Day 82 (Month 3/TC 4), and Monthly Between On-Site Visits through EOS (±7)	On-Site Visits: Day 202 (Month 7/Visit 3), Day 382 (Month 13/Visit 4), and Every 6 Months through EOS (±7)			
Administer/Titrate study drug administration[l]		←	———	———	———	X	——— →			
Study drug compliance/accountability			X	X	X	X	X	X		X
Adverse events[m]	X		X	X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X
ESS	X				X		X	X		
IHSS	X				X		X	X		
FOSQ-10	X				X		X	X		
PROMIS-SRI	X				X		X	X		
SIQ	X				X		X	X		
CGI-S (IH)	X				X		X	X		
PGI-S (EDS)	X				X		X	X		

AE = adverse event; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; EDS = excessive daytime sleepiness; ECG = electrocardiogram; EOS = end-of-study; EOT = end-of-treatment; 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; PGI-S = Patient Global Impression of Severity; PROMIS-SRI = Patient-Reported Outcomes of Measurement Information System, Sleep-Related Impairment; SIQ = Sleep Inertia Questionnaire; TC = telephone contact; Unsch = unscheduled

[a] The Screening Visit (Day -1) for this study is the EOT Visit/Visit 5 from study HBS-101-CL-010; eligibility will be confirmed from the results of assessments completed at this visit, and first day of dosing (Day 1) is to occur up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010. Urine drug screen (dipstick) will also be collected at this visit.

[b] The 3-week Titration Period will be from Day 1 to Day 21; eligible patients will receive their first dose of pitolisant on Day 1, which will be the morning after completion of the Screening Visit or up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 if a patient does not choose to immediately enroll into the open-label, long-term study.

Pitolisant dose may be titrated on Day 8 and on Day 15, up to a maximum of 35.6 mg based on the Investigator's assessment of safety/tolerability and effectiveness. Patients may remain on a lower dose of pitolisant for longer than one week or switch between doses (higher or lower) during the 3-week Titration Period. Patients will receive TCs on Day 8 (TC 1) and Day 15 (TC 2) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug.

[c] At the end of the 3-week Titration Period, patients will continue to take pitolisant once daily in the morning upon wakening in the Long-Term Dosing Period; adjustments to pitolisant dose are permitted during this period. The Long-Term Dosing Period will be from Day 22 until the patient discontinues from the study or the Sponsor elects to terminate the study (i.e., EOS).

[d] Day 1 is the first day of dosing and will occur the morning after the Screening Visit or up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 for eligible patients who do not immediately enroll in the study. There is no visit or TC required on this day.

[e] TCs will be used to assess AEs and concomitant medication use; complete the C-SSRS; and confirm the current dose of study drug, compliance with dosing, and shipment/receipt of study drug sufficient for 3 months (i.e., 90 days) of once daily administration. TCs will occur monthly during the Long-Term Dosing Period and will be conducted between on-site clinic visits.

[f] All patients will complete an EOT Visit for this study. Patients who prematurely discontinue study drug are required to complete the ET Visit; reasons for discontinuation must be recorded.

[g] All patients will receive Safety Follow-Up TCs from the study site 15 (±7) days and 30 (+7) days after their final dose of pitolisant to assess for AEs and concomitant medication use.

[h] 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.

[i] 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.

[j] All 12-lead ECGs will be performed locally using the site's standard ECG equipment. Perform ECGs after the patient has been resting for at least 5 minutes. Any clinically significant ECG value is to be promptly addressed by the Investigator in accordance with the protocol.

[k] Study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration will be provided to eligible patients every 3 months (90 days) either via mail or at on-site study visits; additional study drug may be dispensed between TCs and on-site visits, if necessary.

[l] Eligible patients will take the first dose of open-label pitolisant on Day 1 and will be instructed to take study drug once daily in the morning upon wakening.

[m] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides informed consent through 30 days (+7 days) after final dose of pitolisant. At the Safety Follow-Up TCs, AEs and concomitant medication use will be recorded.

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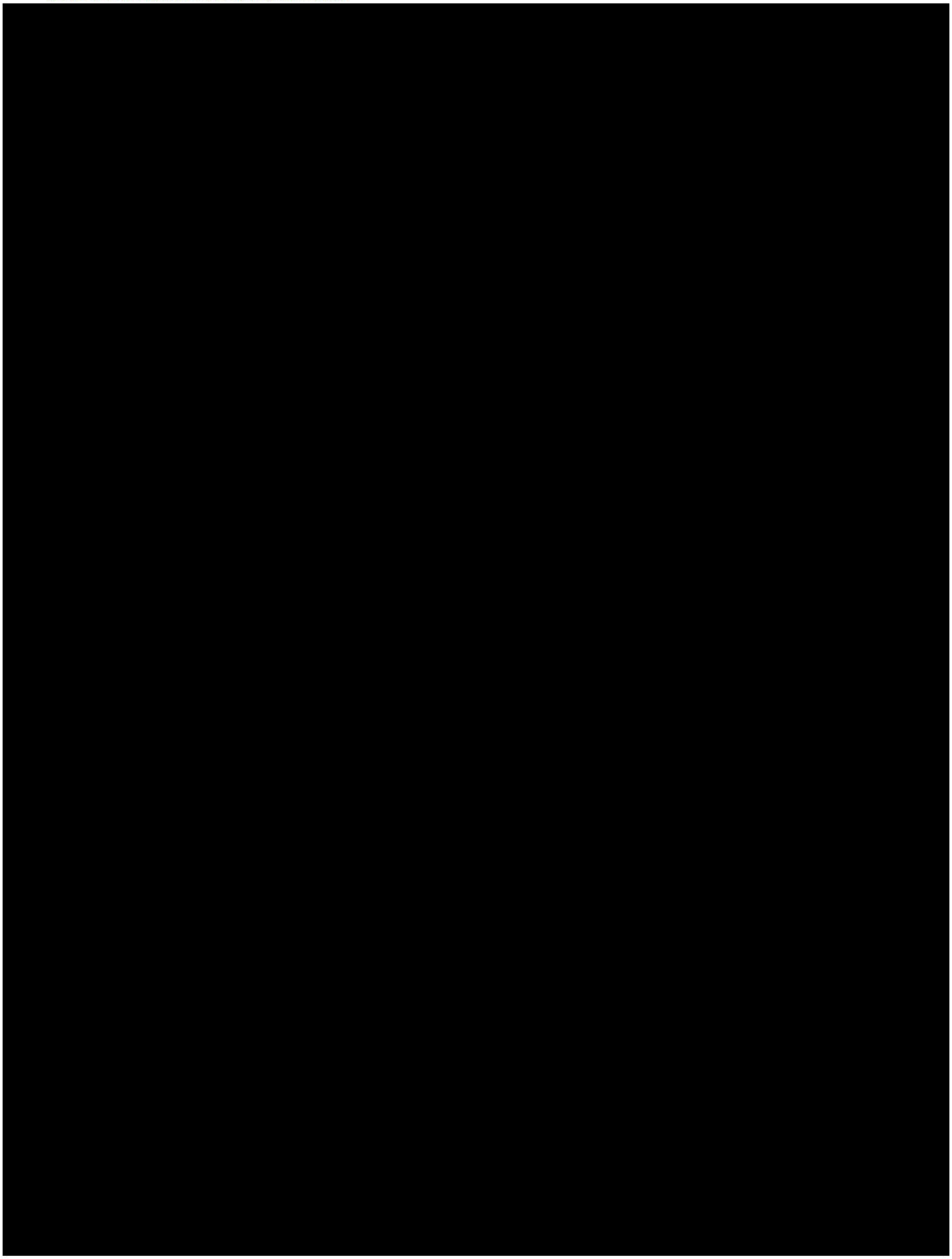
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

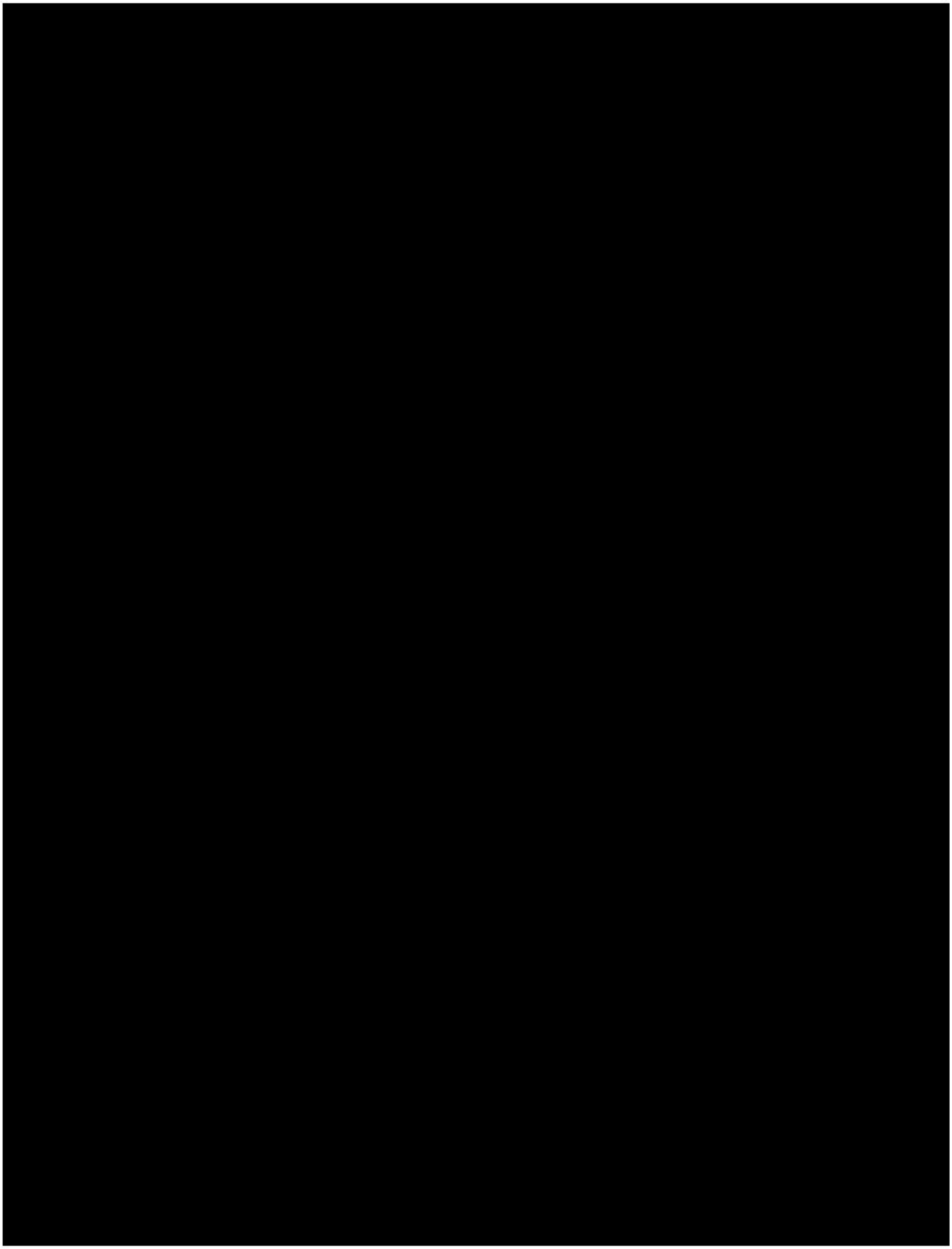
Abbreviation	Definition
AASM	American Academy of Sleep Medicine
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ASP	Average sleep propensity
cGCP	Current Good Clinical Practice
CGI-S	Clinical Global Impression of Severity
CNS	Central nervous system
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDS	Excessive daytime sleepiness
eGFR	Estimated glomerular filtration rate
EOS	End-of-Study
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

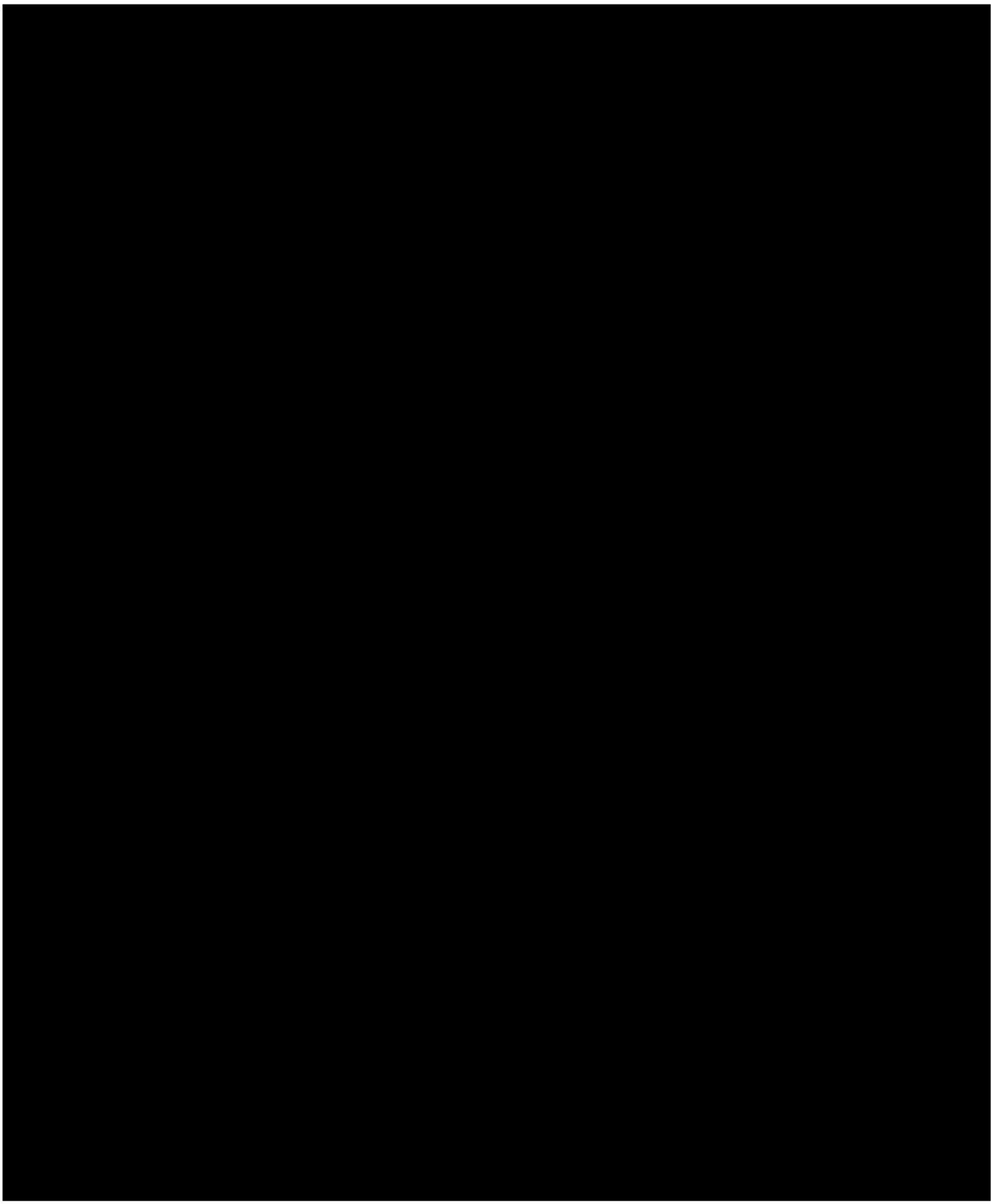
Abbreviation	Definition
GABA	Gamma aminobutyric acid
GCP	Good Clinical Practice
H_1R	Histamine 1 receptor
H_3R	Histamine 3 receptor
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICSD	International Classification of Sleep Disorders
ICSD-2	International Classification of Sleep Disorders Second Edition
ICSD-3	International Classification of Sleep Disorders Third Edition
ID	Identification
IEC	Independent Ethics Committee
IH	Idiopathic hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
ITT	Intent-to-treat
IRB	Institutional Review Board
LSM	Least square mean
MOA	Mechanism of action
MSLT	Multiple Sleep Latency Test
NDA	New drug application
NT1	Narcolepsy type 1
NT2	Narcolepsy type 2
OSA	Obstructive sleep apnea
PGI-S	Patient Global Impression of Severity
PM	Poor metabolizer
PROMIS-SRI	Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment
PSG	Polysomnography
QTc	Corrected QT interval

Abbreviation	Definition
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
SOA	Schedule of assessments
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.







1. 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 2020)
- 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 International Classification of Sleep Disorders (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 Third Edition (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 2020; Trotti 2017b; 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 2020). 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 2020). 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 multiple other countries. 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 2020). 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 2020).

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]

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. A Phase 3 study, HBS-101-CL-010 (i.e., a double-blind, placebo-controlled, randomized withdrawal study), evaluating 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 is ongoing. Study HBS-101-CL-011 is an open-label, long-term, extension study designed to provide data on the long-term safety and effectiveness of pitolisant in this patient population; patients who complete the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 will be eligible to enroll.

1.2. Rationale for Study Design

This open-label, long-term study will allow for eligible patients who complete the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 to receive pitolisant until they discontinue from the study or the Sponsor elects to terminate the study. The study will evaluate long-term safety and effectiveness of pitolisant in this patient population.

1.3. Dose Rationale

The dosing regimen for this long-term study is according to the recommended dosage range for WAKIX (pitolisant), which is 17.8 mg to 35.6 mg administered orally once daily in the morning upon wakening. This is consistent with the current FDA-approved prescribing information for WAKIX 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 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. Patients with ESRD, moderate or severe hepatic impairment, or moderate or severe renal impairment are also excluded.

There was no evidence of withdrawal syndrome from pitolisant or rebound effect upon discontinuation of therapy, and long-term studies did not demonstrate evidence of the development of tolerance to pitolisant. 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 assess the long-term safety and effectiveness of pitolisant in patients with IH who complete the Double-Blind Randomized Withdrawal Phase of Phase 3 study HBS-101-CL-010.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 3 open-label, long-term study to evaluate the long-term safety and effectiveness of pitolisant in adult patients with IH.

Patients (approximately [redacted]) who complete the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010 (i.e., completed the End-of-Treatment [EOT] Visit/Visit 5 in the HBS-101-CL-010 study) and who meet the inclusion/exclusion criteria for study HBS-101-CL-011 are eligible for enrollment. Failure to comply with the Double-Blind Randomized Withdrawal Phase of study HBS-101-CL-010, as determined by the Medical Monitor, will preclude patients from participating in the open-label, long-term study.

The Screening Visit (Day -1) for this open-label, long-term study is the EOT Visit/Visit 5 from study HBS-101-CL-010; the results of assessments performed at this visit will be used to confirm patient eligibility. Patients will have up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 to enroll in this study and begin open-label pitolisant. Enrolled patients may be titrated up to a maximum dose of 35.6 mg pitolisant during a 3-week Titration Period. The decision whether to increase the dose of pitolisant (from 8.9 mg to 17.8 mg and then to 35.6 mg) is made by the Investigator based on their assessment of overall safety/tolerability and effectiveness. If a patient is identified as a cytochrome P450 (CYP) 2D6 PM and had previously received pitolisant at a stable once daily dose of 35.6 mg, the Investigator should consult with the Medical Monitor prior to adjusting the daily pitolisant dose to 35.6 mg or deciding to allow the patient to remain at a once daily pitolisant dose of 35.6 mg. If a patient is identified as a CYP2D6 PM and had not previously received pitolisant at a stable once daily dose of 35.6 mg, the patient may only receive a maximum once daily dose of 17.8 mg.

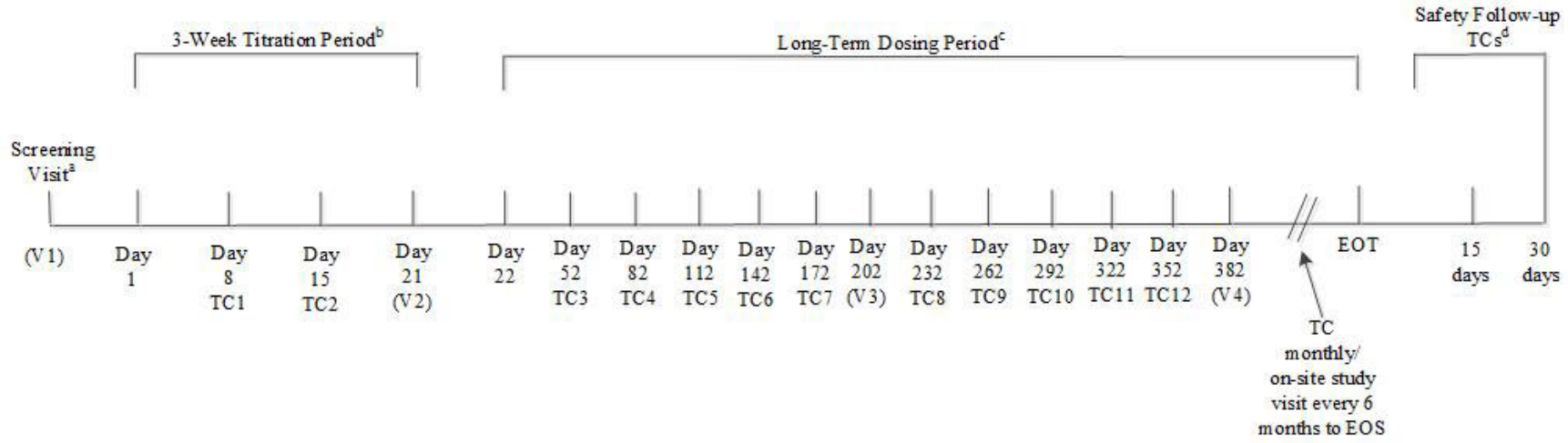
After completion of the Titration Period, patients will continue to receive pitolisant up to 35.6 mg once daily in the morning upon wakening in the Long-Term Dosing Period. During the Long-Term Dosing Period, doses of pitolisant may be adjusted (higher or lower) in increments of 4.45 mg based on Investigator assessment of safety/tolerability and effectiveness. The permitted dose range is from 8.9 mg to 35.6 mg.

The results of assessments performed at the EOT Visit/Visit 5 from study HBS-101-CL-010 will be used as Baseline values for this study.

Further details on eligibility are provided in Section 3.1.2. Further details for the Titration Period and Long-Term Dosing Period (including safety and evaluation of effectiveness) are provided in Section 3.1.3 and Section 3.1.4, respectively.

An overall schema of the study design is provided in Figure 1.

Figure 1: Overall Study Design



AE = adverse event; C-SSRS = Columbia-Suicide Severity Scale; EOS = end-of-study; EOT = end-of-treatment; TC = telephone contact; V = visit.

[a] The Screening Visit (Day -1) for this study is the EOT Visit (Visit 5) from study HBS-101-CL-010; confirmation of eligibility will be determined from the results of assessments completed at this visit.

[b] The 3-week Titration Period will be from Day 1 to Day 21; eligible patients will receive their first dose of pitolisant on Day 1, which will be the morning after completion of the Screening Visit or up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 if a patient does not choose to immediately enroll into the open-label, long-term study. All patients will receive pitolisant and may be titrated up to a maximum dose of 35.6 mg. Pitolisant dose may be titrated on Day 8 and on Day 15. Patients may remain on a lower dose of pitolisant for longer than one week or switch between doses (higher or lower) based on the Investigator's assessment of safety/tolerability and effectiveness during the 3-week Titration Period. Patients will receive TCs on Day 8 and Day 15 (TC 1 and TC 2, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug.

[c] The Long-Term Dosing Period will be from Day 22 until the patient discontinues from the study or the Sponsor elects to terminate the study (i.e., EOS). TCs will occur monthly during the Long-Term Dosing Period and will be conducted between on-site clinic visits. Adjustments to pitolisant dose are permitted during this period.

[d] All patients will receive Safety Follow-Up TCs from the study site 15 days and 30 days after their final dose of pitolisant to assess for AEs and concomitant medication use.

3.1.2. Screening (Day -1) and Eligibility

Patients who complete study HBS-101-CL-010 will have up to 7 days from the EOT Visit/Visit 5 to enroll in study HBS-101-CL-011 and begin open-label pitolisant. The EOT Visit/Visit 5 for study HBS-101-CL-010 is the Screening Visit for study HBS-101-CL-011. Patients will provide written informed consent at the Screening Visit, or informed consent may be provided remotely for patients who do not immediately enroll in the study. The results of assessments performed at this visit will be used to confirm eligibility for study HBS-101-CL-011.

Enrolled patients will be dispensed open-label pitolisant. Patients may be titrated up to a maximum pitolisant dose of 35.6 mg over 3 weeks, as detailed in Section 3.1.3.

3.1.3. Titration Period: Days 1 to 21

The 3-week Titration Period will be from Day 1 to Day 21 (±3 days). Patients may be titrated up to a maximum daily dose of 35.6 mg pitolisant and will be instructed to take pitolisant once daily in the morning upon wakening. If a patient is identified as a CYP2D6 PM and had previously received pitolisant at a stable once daily dose of 35.6 mg, the Investigator should consult with the Medical Monitor prior to adjusting the daily pitolisant dose to 35.6 mg or deciding to allow the patient to remain at a once daily pitolisant dose of 35.6 mg. If a patient is identified as a CYP2D6 PM and had not previously received pitolisant at a stable once daily dose of 35.6 mg, the patient may only receive a maximum once daily dose of 17.8 mg.

Patients will take their first dose of pitolisant (8.9 mg) on Day 1, which is the morning after the Screening Visit or up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010 if a patient does not choose to immediately enroll in this open-label, long-term study. During the 3-week Titration Period, the dose of pitolisant may be titrated on Day 8 and again on Day 15 up to a maximum dose of 35.6 mg, as detailed in Table 3, based on the Investigator's assessment of safety/tolerability and effectiveness. Patients may remain on a lower dose for longer than one week or switch between doses (higher or lower), based on Investigator assessment.

Patients will receive telephone contacts (TCs) from the site on Day 8 (TC 1) and on Day 15 (TC 2) during the Titration Period to assess for adverse events (AEs) and concomitant medication use, complete the Columbia-Suicide Severity Rating Scale (C-SSRS), and review/confirm pitolisant dose titration.

Table 3: Pitolisant Dosing

3-Week Titration Period[a]			Long-Term Dosing Period[b]
Week 1 (Days 1 – 7)	**Week 2 (Days 8 – 14)**	**Week 3 (Days 15 – 21)**	**Week 4 (Day 22) to End-of-Study**
8.9 mg	17.8 mg	35.6 mg	8.9 mg to 35.6 mg

[a] Patients may remain on a lower dose for longer than one week or switch between doses (higher or lower) based on Investigator assessment of tolerability during the Titration Period.
[b] In the Long-Term Dosing Period, patients will continue to receive pitolisant up to 35.6 mg once daily in the morning upon wakening. Pitolisant dose may be adjusted (higher or lower) during the Long-Term Dosing Period (range: 8.9 mg to 35.6 mg) based on Investigator assessment of safety/tolerability and effectiveness.

3.1.4. Long-Term Dosing Period: Day 22 to End-of-Study

After completing the Titration Period, patients will enter the Long-Term Dosing Period. The Long-Term Dosing Period will begin on Day 22 and will continue until the patient discontinues from the study or the Sponsor elects to terminate the study (i.e., End-of-Study [EOS]).

During the Long-Term Dosing Period, patients will continue to take their pitolisant medication once daily in the morning upon wakening; first day of dosing in the Long-Term Dosing Period is on Day 22 (Table 3). Pitolisant dose may be adjusted (higher or lower) during the Long-Term Dosing Period based on Investigator assessment of safety/tolerability and effectiveness as detailed in Section 3.1.5.

Patients will complete an on-site study visit on Day 22 (Visit 2). Patients will receive a TC from the site approximately one month later on Day 52 (TC 3). TCs will occur monthly in between each on-site visit. An on-site study visit will occur approximately 180 days after Visit 2 on Day 202 (Visit 3). On-site study visits will occur approximately every 6 months and TCs approximately every month in between on-site visits until the patient discontinues from the study, or the study is terminated by the Sponsor.

At all on-site study visits (Visit 2 and approximately every 180 days) during the Long-Term Dosing Period, assessments for safety and effectiveness will be performed as detailed in Section 7.3.1. At all TCs (approximately every month) during the Long-Term Dosing Period, AEs and concomitant medications use will be recorded, the C-SSRS will be completed, and the current dose of pitolisant will be confirmed, as detailed in Section 7.3.2.

Pitolisant in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration will be provided to eligible patients every 3 months (i.e., 90 days) either via mail or at the on-site study visits; additional pitolisant may be dispensed between TCs and/or at on-site visits if necessary.

All patients will receive Safety Follow-Up TCs from the study site 15 days and 30 days after their final dose of pitolisant, which will include assessments for AEs and concomitant medication use, as detailed in Section 7.6.

3.1.5. Dose Adjustments

Adjustments in pitolisant dose are permitted in the Long-Term Dosing Period. Pitolisant dose may be adjusted (higher or lower) based on Investigator assessment of safety/tolerability and effectiveness. Decreases in pitolisant dose are permitted at any time at the discretion of the Investigator. For patients who are on less than the maximum once daily dose of pitolisant 35.6 mg, dose increases are at the Investigator's discretion. Discussions and decisions regarding adjustments in pitolisant dose will occur over the telephone or during on-site study visits (either scheduled or unscheduled). It is recommended that adjustments made during this time be to one of the three pre-specified once daily doses of 35.6 mg, 17.8 mg, or 8.9 mg. If deemed necessary by the Investigator, alternate doses may be used in increments of 4.45 mg. The permitted dose range is from 8.9 mg to 35.6 mg.

If a patient is taking a strong CYP2D6 inhibitor, pitolisant dose is to be reduced by one half; if a patient begins taking a strong CYP3A4 inducer during the Long-Term Dosing Period, pitolisant dose may be increased up to the maximum permitted once daily dose of 35.6 mg (Section 5.7.3).

If a patient is identified as a CYP2D6 PM and had previously received pitolisant at a stable once daily dose of 35.6 mg, the Investigator should consult with the Medical Monitor prior to adjusting the daily pitolisant dose to 35.6 mg or deciding to allow the patient to remain at a once daily dose of 35.6 mg. If a patient is identified as a CYP2D6 PM and had not previously received pitolisant at a stable once daily dose of 35.6 mg, the patient may only receive a maximum once daily dose of 17.8 mg.

3.1.6. Dose Interruptions

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

If dosing is interrupted for 7 or more consecutive days, the Investigator should consult with the Medical Monitor before restarting pitolisant.

3.2. Study Endpoints

3.2.1. Safety Endpoints

The long-term safety and tolerability of pitolisant will be evaluated via the incidence of AEs and changes in clinical laboratory test results, vital signs, 12-lead ECGs, and C-SSRS assessments.

3.2.2. Effectiveness Endpoints

Change from Baseline (EOT Visit/Visit 5 in study HBS-101-CL-010) in:

- Epworth Sleepiness Scale (ESS)
- Idiopathic Hypersomnia Severity Scale (IHSS)
- Clinical Global Impression of Severity (CGI-S) for IH
- Patient Global Impression of Severity (PGI-S) for EDS
- Functional Outcomes of Sleep Questionnaire (FOSQ-10)
- Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment (PROMIS-SRI)
- Sleep Inertia Questionnaire (SIQ)

3.3. Study Duration

The study is expected to be multi-year in duration. The study will remain open until all patients discontinue from pitolisant or the Sponsor elects to terminate the study.

The duration of the study for individual patients may be multiyear in duration; all patients will be followed for safety until 30 days after their final dose of pitolisant.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

[redacted]

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, informed consent.
2. Completed the Double-Blind Randomized Withdrawal Phase (EOT/Visit 5) from the HBS-101-CL-010 study.
3. A patient who is a female of child-bearing potential must have a negative urine pregnancy test at the Screening Visit. A patient who is a female of child-bearing potential must 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.
4. Must have a negative result on urine drug screen at the Screening Visit, except for medications that are prescribed by a healthcare provider for medical conditions.
5. 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. Does not agree to discontinue any prohibited medication or substances listed in the protocol.
2. 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.
3. Participation in an interventional research study with an investigational medication or device, other than pitolisant, for the duration of the study.
4. 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).
5. Is receiving or is unable to discontinue a medication known to prolong the QT interval.
6. Has a significant risk of committing suicide or suicidality based on history; routine psychiatric examination; Investigator's judgment; or who has an answer of "yes" on [redacted] or "yes" on [redacted] in the suicidal behavior section of the C-SSRS, Since Last Visit.

7. 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.

4.2. Method of Assigning Patients to Treatment

Patients who meet all eligibility criteria will be assigned a unique identification (ID) number prior to dosing using electronic data capture (EDC).

4.2.1. Procedures for Handling Enrolled 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.

4.3. Blinding

Blinding is not applicable in this open-label study.

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:
  - QTcF >500 msec
  - or
  - QTcF increase from Screening (Visit 1) of study HBS-101-CL-010 >60 msec and QTcF >470 msec

Any ECG finding that demonstrates QT prolongation 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.

[redacted]

The date and primary reason for early withdrawal will be recorded in the electronic case report form (eCRF). At the time of withdrawal from the study, every attempt should be made to complete the Early Termination (ET) Visit assessments (Section 7.5).

4.4.2. Procedures for Patient Follow-up

Patients will receive two Safety Follow-Up TCs from the site, one at 15 days and the second at 30 days after their last dose of open-label pitolisant, to assess for AEs and concomitant medication use as detailed in Section 7.6.

Patients who prematurely discontinue pitolisant are required to undergo the assessments in the ET Visit, and the reasons for discontinuation must be recorded (Section 7.5). 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 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 study will not 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 their final dose of pitolisant.

4.6.2. Patient Completion

Patients who do not withdraw from the study prior to study termination and complete the second Safety Follow-Up TC at 30 days after their final dose of study drug will be considered to have completed the study.

4.7. Screen Failures

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

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

5. STUDY TREATMENT

5.1. Description of Study Drug

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

5.2. 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 will be provided to patients as individual bottles containing pitolisant 4.45 mg or 17.8 mg tablets.

5.3. Storage

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

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

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

5.4. Study Drug Administration

Patients will take open-label pitolisant once daily in the morning upon wakening as detailed in Table 3. 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 during on-site study visits by conducting tablet counts based on the returned study drug. During the TCs, compliance will be monitored by confirming the patient's current dose of study drug and adherence to dosing, as well as shipment/receipt of study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration.

5.6. Study Drug Accountability

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

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

5.7. Prior and Concomitant Therapy

Prior medications in the patient's medical record (including any medications taken during study HBS-101-CL-010) and prior medications reported by the patient will be collected.

Concomitant medications reported by the patient will be collected. Concomitant medications include prescription and over the counter medications (including herbal products and vitamins) taken while in this study.

All medications taken by patients between signing of informed consent for this study and the second Safety Follow-Up TC (30 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 dose 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.

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

Pitolisant increases the levels of histamine in the brain; therefore, centrally acting H_1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of pitolisant. Concomitant use of centrally acting H_1 receptor antagonists should be avoided and, if needed, will require consultation with the Medical Monitor.

Examples of centrally acting H_1R antagonists and medications that may prolong the QT interval are provided in Appendix A.

5.7.3. Medications Requiring Adjustment to the Dose of Pitolisant

The use of medications known to be strong CYP2D6 inhibitors or strong CYP3A4 inducers is allowed in the Long-Term Dosing Period; however, if used, the following adjustments to the dose of pitolisant apply:

- Strong CYP2D6 inhibitors: Systemic exposure of pitolisant is increased 2.2-fold in the presence of strong CYP2D6 inhibitors. If initiating treatment with a strong CYP2D6 inhibitor, pitolisant dose should be reduced by half. Maximum permitted dose of pitolisant is 17.8 mg.
- Strong CYP3A4 inducers: Systemic exposure of pitolisant is reduced by 50% in the presence of strong CYP3A4 inducers. If initiating treatment with a strong CYP3A4 inducer, clinical symptoms should be monitored, and pitolisant dose may need to be increased. Pitolisant dose may only be increased up to the maximum permitted dose of 35.6 mg.

Examples of strong CYP2D6 inhibitors and strong CYP3A4 inducers are provided in Appendix A.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. Additional information about the timing of assessments is provided in Section 7 and in the Schedule of Assessments (SOA).

6.1. Medical History and Demographics

6.1.1. Medical History

Medical history collected in study HBS-101-CL-010 will be updated at the Screening Visit and as necessary thereafter. Adverse events that occurred in study HBS-101-CL-010 and are ongoing at the start of this study will be recorded as medical history.

6.1.2. Demographic Information

Demographic information (date of birth, sex, race, and ethnicity) collected at Screening in study HBS-101-CL-010 will be used for this study.

6.2. Effectiveness Assessments

Effectiveness of pitolisant will be evaluated using the ESS, IHSS, CGI-S (IH), PGI-S (EDS), FOSQ-10, PROMIS-SRI, and SIQ. The timing of these evaluations is presented in the SOA and in Section 7.

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 B.

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 C.

6.2.3. 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) 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 D.

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

The PROMIS-SRI is a subjective measure that includes several 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 – Short Form 8a questionnaire will be used in this study and is provided in Appendix E.

6.2.5. 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 F.

6.2.6. Clinical Global Impression of Severity (CGI-S) for Idiopathic Hypersomnia

Clinician overall assessment of disease severity will be measured using the CGI-S (IH). The CGI-S (IH) 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]

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

Patient overall assessment of EDS will be measured using the PGI-S (EDS) at Screening and at all on-site visits. [redacted]

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 physical examinations will be performed at study visits as detailed in Section 7. Physical examinations will include an evaluation of the head and neck as well as cardiovascular, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems.

Body weight will be measured using standardized methods at every on-site visit.

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 Electrocardiograms

Single 12-lead ECGs will be performed as detailed in Section 7. Patients should be resting for at least 5 minutes before the ECG is performed 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 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 (urine), and urine drug screens (dipstick) as detailed in Table 4. 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 total volume of blood collected 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 4: Clinical Laboratory Tests

Drug Screen (Urine) – dipstick -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 **Urine Pregnancy Screen (FCBP only)**	**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=female of childbearing potential, HbA1C = hemoglobin A1C; WBC = white blood cell.

6.3.6. Columbia-Suicide Severity Rating Scale

Suicide risk and suicidality will be evaluated at all study visits and TCs through use of the C-SSRS, Since Last Visit (Appendix I). 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).

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 (Day -1)

Patients will provide written informed consent at the Screening Visit (informed consent may be provided remotely for patients who do not immediately enroll in the study, i.e., up to 7 days from EOT Visit/Visit 5 for study HBS-101-CL-010), and eligibility will be based on results of assessments performed at the Screening Visit.

The following assessments will be completed:

- Medical history (Section 6.1.1)
- Demographics (Section 6.1.2)
- Urine pregnancy test (FCBP only)
- Urine drug screen (dipstick)
- Full physical examination
- Body weight
- Vital signs
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- 12-lead ECG
- C-SSRS, Since Last Visit
- AEs (since providing informed consent for this study)
- Concomitant medications (since providing informed consent for this study)
- ESS
- IHSS
- CGI-S (IH)
- PGI-S (EDS)
- FOSQ-10
- PROMIS-SRI
- SIQ

Enrolled patients will be dispensed pitolisant and will be instructed to take pitolisant once daily in the morning upon wakening.

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

7.2. Titration Period (Day 1 to Day 21)

Section 3.1.3 provides details on pitolisant dosing in the Titration Period.

During the Titration Period, patients will be contacted by the study site by telephone on Day 8 and Day 15 (TCs 1 and 2, respectively) to assess for AEs and concomitant medication use, complete the C-SSRS, and review/confirm pitolisant titration and compliance.

7.3. Long-Term Dosing Period (Day 22 to End-of-Study)

Patients will continue to take pitolisant at their optimal dose (based on Investigator assessment of safety/tolerability and effectiveness) during the Long-Term Dosing Period as detailed in Section 3.1.4, with dosing adjustments permitted as detailed in Section 3.1.5.

Patients will complete an on-site study visit on Day 22 (Visit 2; first day of dosing in the Long-Term Dosing Period) for assessment of safety/tolerability and effectiveness as detailed in Section 7.3.1. After completion of Visit 2, patients will receive a TC from the study site on Day 52 (TC 3) and thereafter approximately every one month (30 days) in between on-site visits for assessment of safety as detailed in Section 7.3.2. Patients will return to the study site on Day 202 (Visit 3) and approximately every 6 months (180 days) thereafter for assessment of safety and effectiveness as detailed in Section 7.3.1. This pattern of monthly TCs in between on-site study visits will be repeated until EOS.

7.3.1. Study Visits: Visit 2 (Day 22), Visit 3 (Day 202), and all Study Visits Thereafter (Every 180) until End-of-Study

Except where specified, patients will complete the following assessments at Visit 2 and at all on-site study visits thereafter:

- Urine pregnancy test (FCBP only)
- Urine drug screen; not performed at Visit 2
- Full physical examination
- Body weight
- Vital signs
- Clinical laboratory tests (serum chemistry, hematology, urinalysis); not collected at Visit 2
- 12-lead ECG; not performed at Visit 2
- C-SSRS, Since Last Visit
- Review of AEs
- Review of concomitant medications
- ESS
- IHSS
- CGI-S (IH)

- PGI-S (EDS)
- FOSQ-10
- PROMIS-SRI
- SIQ
- Review study drug compliance/accountability
- Confirm study drug dose

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

7.3.2. Telephone Contacts: TC 3 (Day 52) and all TCs Thereafter until End-of-Study

Patients will complete all of the following assessments at TC 3 and all TCs thereafter:

- C-SSRS, Since Last Visit
- Review of AEs
- Review concomitant medications
- Review study drug compliance/accountability
- Confirm study drug dose

During the TCs, every 90 days the study site will confirm shipment/receipt of the patient's 3-month (90-day) supply of study drug

7.4. End-of-Treatment Visit

All patients will complete an EOT Visit after they complete treatment with pitolisant; the following assessments will be completed:

- Urine pregnancy test (FCBP only)
- Full physical examination
- Body weight
- Vital signs
- Clinical laboratory tests (serum chemistry, hematology, urinalysis)
- 12-lead ECG
- C-SSRS, Since Last Visit
- Review of AEs
- Review of concomitant medications
- ESS
- IHSS
- CGI-S (IH)

- PGI-S (EDS)
- FOSQ-10
- PROMIS-SRI
- SIQ
- Review study drug compliance/accountability
- Collect all unused study drug

7.5. Early Termination Visit

Every effort should be made to perform the ET Visit evaluations for patients who prematurely discontinue study drug. Assessments for the ET Visit are the same as those listed for the EOT Visit; the reason for early termination must be recorded.

7.6. Safety Follow-Up Telephone Contacts

All patients will receive a Safety Follow-Up TC from the study site 15 days and 30 days after their final dose of pitolisant to assess for AEs and concomitant medication use.

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 and Section 5.6, respectively)

Other assessments (e.g., 12-lead ECGs, clinical laboratory tests, urine pregnancy test, C-SSRS) 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 make an assessment of causality. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality based on follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides informed consent through 30 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 screening values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The patient is lost to follow-up, and the status of the event is unknown.
- **Death**

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

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

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

- AE record
- Medical history
- Prior and concomitant medications

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

In rare circumstances and in the absence of email capacity, a copy of the SAE reporting form may be sent to the Sponsor by overnight courier. Initial notification via telephone or email does not replace the need for the Investigator to complete and submit the appropriate SAE form within the time frames outlined.

If the Investigator does not have all information regarding an SAE, they 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 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, they must notify the Sponsor **within 24 hours of becoming aware of the problem**.

The following information should be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence can be reported and legal obligations and ethical responsibilities regarding the safety of other patients are met.

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

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

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

8.4.4. Pregnancy Reporting

Pregnancy is not considered an SAE; however, it is documented and followed in the same manner as an SAE. Any patient who becomes pregnant during the study must be withdrawn from

the study immediately. Patients who become pregnant within 30 days after receiving their final dose of study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on the outcome and health status of the mother and child.

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

9. STATISTICS

9.1. General Considerations

All safety and effectiveness data will be listed and summarized. Only data related to the HBS-101-CL-011 open-label study will be reported. Demographics and baseline characteristics for patients who received at least one dose of open-label pitolisant in study HBS-101-CL-011 will be reported. Baseline will be defined as EOT Visit/Visit 5 from study HBS-101-CL-010.

If the statistical analyses described in the final SAP and final protocol differ, the statistical analyses in the SAP will be used for analyses presented in the CSR. Substantive changes from the analyses originally specified in the protocol will be described in the SAP and in the final CSR.

9.2. Determination of Sample Size

[redacted]

9.3. Analysis Populations

9.3.1. Safety Population

The safety population will include all patients who are enrolled and take at least one dose of open-label pitolisant in study HBS-101-CL-011.

9.4. Statistical Analysis Methods

All analyses will be reported by the treatment received in the Double-Blind Withdrawal Phase of study HBS-101-CL-010 and overall.

9.4.1. Disposition and Demographics

The number of patients completing study HBS-101-CL-010, number of patients enrolled in study HBS-101-CL-011, number and percentage of patients completing study HBS-101-CL-011, and number and percentage of patients discontinuing from study HBS-101-CL-011 (including reasons for discontinuation) will be summarized. All percentages will be calculated using the number of patients enrolled as the denominator.

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

9.4.2. Effectiveness Analysis

The effectiveness outcome measures will be measured at Screening and at all on-site visits. Effectiveness outcome measures include ESS, IHSS, CGI-S (IH), PGI-S (EDS), FOSQ-10, PROMIS-SRI, and SIQ.

Summary statistics will be reported for continuous study assessments at all timepoints (i.e., mean, SD, median, minimum, maximum). Both the raw values and changes from baseline (where applicable) will be summarized.

9.4.3. Safety Analysis

All safety analyses will be completed for the Safety Population. All safety data will be listed and summarized. No formal inferential statistics will be performed for the safety analysis.

Safety will be assessed by monitoring and recording all AEs and concomitant medications, starting with the first dose of open-label pitolisant in study HBS-101-CL-011 and through 30 days after final dose of study drug (Safety Follow-Up TCs, Section 7.6).

A TEAE is defined as:

- Any AE reported after the first dose of open-label pitolisant in study HBS-101-CL-011 and up to 30 days after final dose of open-label pitolisant in study HBS-101-CL-011
- Any worsening of a pre-existing condition reported after the first dose of open-label pitolisant in study HBS-101-CL-011 and up to 30 days after the final dose of open-label pitolisant in study HBS-101-CL-011

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 drug discontinuation and 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.

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, informed consent form (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, emails, and letters in order to review study progress and eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: patients' informed consent 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 IRBs/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 will provide the Sponsor with sufficient, accurate financial information as required to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.4. Suspension or Termination of Study or Investigational Site

12.4.1. Suspension of Study

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

12.4.2. Termination of Study or Investigational Site

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

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

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

12.5. Publication and Information Disclosure Policy

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

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

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

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

When the study is completed or prematurely terminated, the Sponsor or designee will ensure a clinical study report (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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APPENDIX A. EXAMPLES OF STRONG CYP2D6 INHIBITORS, STRONG CYP3A4 INDUCERS, CENTRALLY ACTING H_1R 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
Centrally acting H_1R antagonists	pheniramine maleate, diphenhydramine, promethazine (antihistamines), imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)

CYP = cytochrome P450; H_1R = histamine 1 receptor.

APPENDIX B. 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 C. 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 D. 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?	❒	❒	❒	❒	❒

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	(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.

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

PROMIS® Item Bank v1.0 – Sleep-Related Impairment – 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 F. 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 G. CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGI-S) FOR IDIOPATHIC HYPERSOMNIA



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



APPENDIX I. 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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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

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
____

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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