A Phase 2, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study to Determine the Safety and Efficacy of Oral SDX in Patients with Idiopathic Hypersomnia (IH)

Protocol No: KP1077.D01

Version: 4.0

A Phase 2, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study to Determine the Safety and Efficacy of Oral SDX in Patients with Idiopathic Hypersomnia (IH)

Sponsor & Principal Investigator Approval / Signature Page

Protocol Number	KP1077.D01
Protocol Version Date	March 6, 2023
Version Number	4.0
Investigational Product	SDX - Serdexmethylphenidate (KP1077)
IND Number	159433
Study Phase	Phase 2
Sponsor	Zevra Therapeutics (formerly KemPharm, Inc) 1180 Celebration Blvd, Suite 103 Celebration, FL 34747 Phone: 321-939-3416
Principal Investigator	Christopher Drake, PhD, FAASM, DBSM 30551 Club House Lane Farmington Hills, MI 48334 Phone: 248-890-1588
Medical Monitor	Ihab Abdel Fattah, MD, PhD, MSc Rho, Inc 2635 E NC Hwy 54 Durham, NC 27713 Phone: 919-595-6461 (Medical Monitor Line – 8 am-8 pm Mon-Fri (non-holiday)) Email: MedicalMonitorSupport@rhoworld.com, with cc to Ihab_AbdelFattah@rhoworld.com

Digitally signed by Rene Braeckman
Date: 2023.03.06 17:06:18 -05'00'

Rene A. Braeckman, PhD
Vice President of Clinical Development
Zevra Therapeutics

Date

03/07/2023

Christopher Drake, PhD, FAASM, DBSM
Director of Research, Henry Ford Health System
Principal Investigator

Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADL	Activity of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AHI	Apnea Hypopnea Index
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
β-hCG	Beta-human chorionic gonadotropin
bid	Twice a day
BLQ	Below the limit of quantification
BMI	Body Mass Index
BP	Blood Pressure
BZRA	Benzodiazepine receptor agonist
CDH	Central disorder of hypersomnolence
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions–Severity
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus 2 (SARS-CoV-2)
CPAP	Continuous positive airway pressure
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
EOS	End of Study
ePRO	Electronic Patient-Reported Outcomes
ER	Extended Release
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GHB	Gamma-hydroxybutyrate; oxybate

HAP	Human Abuse Potential
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICSD	International Classification of Sleep Disorders
IEC	Independent Ethics Committee
IH	Idiopathic Hypersomnia
IHSS	IH Severity Scale
IND	Investigational New Drug
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
MAOIs	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary of Regulatory Activities
Mod-KSS	Modified Karolinska Sleepiness Scale
MPH	Methylphenidate
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NIH	National Institutes of Health
NCE	New Chemical Entity
OTC	Over the Counter
PD	Pharmacodynamic
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PLMD	Periodic Limb Movement Disorder
PLMA-I	PLMD Arousal Index
POTS	Postural Orthostatic Tachycardia Syndrome
PP	Per-Protocol
PRO	Patient-Reported Outcome
PROMIS®-29	Patient-Reported Outcomes Measurement Information System
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSQI-Q6	Question #6 of the Pittsburgh Sleep Quality Index
qd	Once a day
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTcB	QT interval corrected for heart rate with Bazett’s formula
QTcF	QT interval corrected for heart rate with Fridericias’s formula
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDX	Serdexmethylphenidate

SIVAS	Sleep Inertia Visual Analog Scale
SOE	Schedule of Events
SOREMP	Sleep Onset REM Periods
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to achieve the maximum observed plasma concentration
TNT	Total Nap Time
TSH	Thyroid Stimulating Hormone
TST	Total Sleep Time
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
VT	Ventricular Tachycardia
WPA	Wake-Promoting Agents
ZOGIM-A	Patient-Reported Wakefulness Questionnaire

PROTOCOL SYNOPSIS

TITLE	A Phase 2, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study to Determine the Safety and Efficacy of Oral SDX in Patients with Idiopathic Hypersomnia (IH)
SPONSOR	Zevra Therapeutics (formerly KemPharm, Inc.)
PROTOCOL NUMBER	KP1077.D01
INVESTIGATIONAL PRODUCT	Serdexmethylphenidate (SDX)
NAME OF ACTIVE INGREDIENT	SDX Cl: 3-(((S)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((R)-2-((R)-2-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridine-1-ium chloride.
ROUTE	Oral
NUMBER OF SITES	Approximately 45 sites
STUDY DESIGN	The study is a Phase 2, placebo-controlled, double-blind, randomized withdrawal study to determine the safety and efficacy of oral SDX in patients with Idiopathic Hypersomnia (IH). See Section 2 for the design schematic. The study will consist of the following visits: • **Screening Period**: Subjects will undergo a screening period up to 35 days prior to entering the Open-Label Randomized Titration Period. • **Open-Label Titration Period:** Subjects will attend weekly clinic visits for a period of 5 weeks. The subject's treatment will be titrated (change of dose as needed) to an optimal daily dose of SDX starting with the lowest dose, based on individual tolerability and effect. The 4 possible SDX doses to be taken orally are: o 80 mg/day SDX o 160 mg/day SDX o 240 mg/day SDX o 320 mg/day SDX The subjects will be randomized to one of the following dosing regimens: o **Treatment X:** SDX, once daily at night (qd pm) o **Treatment Y:** SDX, half the daily dose in the morning and at night (bid) Randomization will be stratified by gender. • **Double-Blind Withdrawal Period**: This period will consist of 2 weeks during which the subjects will receive the optimized dose. The subjects will have clinic visits at the beginning and end of the period. At the start of the Withdrawal Period, subjects within each treatment group of the Titration Period will be randomized in a 2:1 ratio

	to SDX or placebo. ○ Subjects receiving Treatment X in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period: ▪ **Treatment A:** SDX, once daily at night (qd pm) ▪ **Treatment B:** Placebo, once daily at night (qd pm). ○ Subjects receiving Treatment Y in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period: ▪ **Treatment C:** SDX, half the daily dose in the morning and at night (bid). ▪ **Treatment D**: Placebo, half the daily dose in the morning and at night (bid). The randomization will be stratified by optimized dose. Subjects will keep taking study drug qd pm or bid (pm and am) as assigned by the randomization at the start of the Titration Period. • **Follow-Up Phone Call**: 1 week after administration of the last dose of the Double-Blind Randomized Withdrawal period, site staff will conduct a follow-up phone call with the subject to evaluate safety parameters.
PRIMARY OBJECTIVE	To determine the safety and tolerability of SDX in treating adults with IH.
SECONDARY OBJECTIVES	• To explore the efficacy of SDX in adults with IH. The study may inform about the best dosing regimen, optimal dose range, duration of treatment, and secondary endpoints for a future Phase 3 study. • To characterize the steady-state pharmacokinetics (PK) following administration of SDX in subjects with IH.
NUMBER OF SUBJECTS	An appropriate number of subjects will enter the Screening Period and complete the Titration Period, to randomize at least 48 subjects (24 subjects for each dosing regimen) in the Withdrawal Period. Screening and enrollment of new subjects will continue until at least 48 subjects are randomized in the Withdrawal Period. The required number of subjects may be increased based on the interim analysis.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** 1. Male or female at least 18 years of age at the time of consent. 2. Subject's Body Mass Index (BMI) must be $\leq$35 kg/m^2. 3. Has a primary diagnosis of IH (lifetime) according to the International Classification of Sleep Disorders (ICSD-3) criteria. If documentation of IH diagnosis is unavailable in the screening window, diagnostic testing

	must be performed according to the ICSD-3 criteria. This may include one of the following to confirm the diagnosis of IH: a. Nocturnal polysomnogram (PSG) followed by a multiple sleep latency test (MSLT). The duration of the MSLT must be long enough to include at least 4 naps b. 24-hour PSG c. Wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep). 4. At the Screening Visit and Visit 2, subjects must have Epworth Sleepiness Scale (ESS) scores ≥11 (as assessed with a look-back period of 1 week). 5. Average nightly Total Sleep Time (TST) of ≥7 hours, per subject history. The average nightly TST will be confirmed by Investigator's review of daily sleep diaries collected during the 10 days before Visit 2 (during the last 10 days of the Screening Period). 6. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis) at Screening. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant. 7. Subjects must give written consent. 8. If currently treated with nicotine replacement therapy, must have been taking the same regimen and dose for at least 2 months prior to screening and must agree to take the same dose during the Titration Period and Withdrawal Period. 9. Subjects must be able and willing to wash out prohibited medications to treat IH and all medications that can affect wakefulness and sleep, including herbal medications. If a subject has received any of the therapies listed in this protocol, a washout-period of at least 14 days, or equivalent to 5 half-lives of the drug, whichever is longer (and at least 30 days for sedating antidepressants; 14 days for CNS stimulants), is required prior to the first dose of study drug. Subjects must abstain from these medications during the study

	until Follow-Up or Early Termination. Patients may be switched from a sedating to a non-sedating antidepressant as long as the switch occurs at least 14 days before Visit 2. 10. Have used a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception. Female subjects must agree to use one of the following forms of birth control from Screening until at least 30 days after the last dose of study drug, unless a different timeframe is listed below: a. Vasectomized partner (at least 6 months prior to Screening). b. Post-menopausal (no menses for at least 12 months prior to Screening). c. Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to Screening. d. Non-surgical sterilization (eg, Essure® procedure) at least 3 months prior to Screening. e. Double barrier (diaphragm with spermicide; condoms with spermicide) f. Intrauterine device (IUD) g. Total abstinence (must agree to use a double barrier method if they become sexually active between Screening and 30 days after the last dose of study drug). h. Implanted or intrauterine hormonal contraceptives in use for at least 3 consecutive months prior to Screening. i. Oral, patch, or injected contraceptives, or vaginal hormonal device (ie, NuvaRing®), in use for at least 3 consecutive months prior to Screening. 11. Male subjects must have had a vasectomy (at least 6 months prior to Screening) or must agree to use one of the following forms of birth control from Screening until 90 days after the last dose of study drug: a. Double barrier method (diaphragm, condoms, contraceptive sponge, or vaginal ring, all with spermicidal jelly or cream). b. Total abstinence (must agree to use a double barrier method if they become sexually active during the

	period from screening to 90 days after the last dose of study drug) 12. Subject must understand and be willing and able to comply with all study procedures and visit schedule, including completion of all forms and questionnaires that the subject will need to fill in daily while at home. **Exclusion Criteria** 1. Hypersomnia due to another medical, behavioral, or psychiatric disorder condition (eg, narcolepsy, depression disorders, multiple sclerosis, Parkinson's disease, stroke). This includes history of cataplexy, history or screening MSLT showing ≥2 Sleep Onset REM Periods (SOREMPs), or history or screening PSG SOREMP <15 minutes. 2. Evidence of clinically significant sleep-related breathing disorders, including any of the following: a. Presence of clinically significant (moderate or worse) obstructive or central sleep apnea as determined by the Investigator or documented within the last 10 years. b. Current diagnosis of clinically significant sleep apnea including being treated with Continuous Positive Airway Pressure (CPAP) therapy or any other treatment of sleep apnea. c. Obstructive Apnea Hypopnea Index (AHI) >15 episodes per hour on any test within the last 10 years or during the Screening PSG (if conducted). d. Clinically significant hypoventilation. 3. Clinically significant parasomnias (eg, sleep walking, rapid eye movement [REM] sleep behavior disorder, etc). 4. Periodic Limb Movement Disorder (PLMD) Arousal Index (PLMA-I) >15 during the Screening PSG (if performed) or from a test during the last 10 years (ie, historical diagnosis of PLMD), or a PLMD diagnosis older than 10 years with current (last 60 days) treatment or symptoms of rhythmic movements involving one or both legs during sleep. 5. Occupation requiring nighttime shift work or variable shift work with early work start times (ie, before 6 AM), if this occurs more than once per week.

	6. Any planned travel during the study that includes more than 3 time zones, or planned travel that includes 3 time zones on more than 2 occasions during the study. 7. Going to sleep for the night later than 1 AM at a frequency of more than once per week. 8. Current or past (within 1 year) major depressive episode according to DSM-5 criteria. Patients with depression under control are allowed per the judgment of the Investigator, but the antidepressant treatment must be non-sedating, stable for at least 6 months prior to Screening and expected to remain stable for the duration of the study. 9. Has any history of attempted suicide (lifetime) or clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment at Screening. 10. Any clinically significant unstable medical abnormality, chronic disease (eg, asthma or diabetes), or a history of a clinically significant abnormality of the cardiovascular (including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension), central nervous system (eg, neurodegenerative disease, seizure disorder or history of head trauma associated with loss of consciousness), gastrointestinal, respiratory (eg, compromised respiratory function), hepatic, or renal systems, or a disorder or history of a condition (eg, malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion of study drug. Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if controlled) must be discussed with and approved by the Medical Monitor during Screening. 11. Subject should be excluded from the study with any of the following vital signs at Screening: a. a confirmed systolic blood pressure outside the range of 90-145 mmHg b. a confirmed diastolic blood pressure outside the range of 50-90 mmHg c. a confirmed resting heart rate outside the range of 40-100 beats per minute

	12. History or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant, including the following: a. ECG findings of ischemia or infarct b. Complete bundle branch blocks c. Symptomatic arrhythmias as ventricular arrhythmias (non-sustained ventricular tachycardia (VT), multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal or any predominantly non-sinus-conducted rhythm. d. QTcF >450 msec for males or >470 msec for females, on Screening ECG. e. PR interval outside the range of 120 to 220 msec on Screening ECG. 13. Estimated glomerular filtration rate (GFR) at Screening <60 mL/min/1.73 m^2 using the CKD-EPI 2009 method. 14. Malignant neoplastic disease requiring therapy within 2 years prior to Screening or during the study, or clinically relevant as judged by the Investigator. 15. Uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening. 16. Laboratory value for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limits of normal (ULN). 17. Excessive caffeine use during the 10 days prior to Visit 2 or anticipated excessive use defined as >600 mg/day of caffeine during the Titration Period and Withdrawal Period. 18. Treatment or planned treatment with prohibited medications (see Section 10) or unwilling to refrain from any prohibited medications. Treatment must have been discontinued 14 days or 5 half-lives, whichever is longer, prior to the first dose of study medication (and at least 30 days for sedating antidepressants; at least 14 days for CNS stimulants). The Investigator must ensure that discontinuation from these medications is medically supervised. 19. Current or past substance use disorder (including alcohol and psychoactive cannabinoids) according to DSM-5 criteria; current or past history of substance abuse treatment (including alcohol), or the subject is

	unwilling to refrain from substance use (including alcohol) during the study. Past is defined as within 12 months prior to Screening. 20. Nicotine dependence that has an effect on sleep (eg, a subject who routinely awakens at night to smoke). 21. Evidence of substance or alcohol use or has a positive urine or breath alcohol or positive urine drug screen at Screening. Urine or breath will be tested for alcohol, and urine will be tested for drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone) and methylphenidate (MPH) at Screening (Visit 1) and at Visit 2. A urine dipstick will be used to screen for the presence of MPH in the urine. Subjects with a positive urine drug screen (eg, amphetamines, methylphenidate) may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required (test at Visit 2 needs to be negative). Subjects with a positive drug test at Screening may be rescreened (test at Visit 2 needs to be negative). 22. Female subjects who are pregnant, breastfeeding, or lactating, or plan to become pregnant during the duration of the study. 23. Participation in any other clinical study with an investigational drug/product within 30 days prior to Screening or is currently participating in another clinical trial. 24. Subject has poor ePRO compliance during the last 10 days of the Screening Period (evaluated at Visit 2), at the discretion of the Investigator. 25. Subject has commitments during the study that would interfere with attending study visits. 26. Subject anticipates a move outside the geographic range of the investigative site during the study period or plans extended travel inconsistent with the planned study visits. 27. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study. **Rescreening** Subjects may be allowed to rescreen if they previously did not meet all eligibility requirements at the Screening Visit.

	Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, uncontrolled thyroid disorder, electrolyte abnormalities) and with the approval of the Investigator. Only those screening procedures that did not meet the eligibility criteria need to be repeated, may only be repeated once, and need to be repeated within the screening window. If a PSG/MSLT was performed during the Screening Period, it will be done only once (no rescreen unless performed with errors). Subjects who failed screening due to a Total Sleep Time of <7 hours based on the sleep diaries collected during the 10 days prior to Visit 2, will not be rescreened. Subjects who have exceeded the time window allowed for screening to complete all screening assessments or have failed some of the inclusion/exclusion criteria with no time left to rescreen within the screening window, may be rescreened (full rescreen) for participation later during the enrollment phase of the study, at the discretion of the Investigator. This full rescreen may be conducted once. Subjects who received any dose of study drug and are terminated early, are not eligible to participate later in the study (and will not be rescreened).
ELIGIBILITY CRITERIA FOR WITHDRAWAL PERIOD	Subjects are eligible to continue in the Withdrawal Period of the study if the following criteria are met at the end of the Titration Period: 1. Subjects demonstrate adequate compliance with dosing in the Titration Period. 2. No ongoing AEs occur due to SDX treatment that would require dose adjustment or early discontinuation during the Withdrawal Period. 3. Subjects must have a decrease of their ESS score of at least 2 points at Visit 7 compared to the titration baseline (Visit 2). Subjects who are not eligible to continue in the Withdrawal Period will be withdrawn, and Early Termination procedures will be completed during an Early Termination visit. The reason for lack of eligibility will be recorded.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	The following daily doses of study drug will be administered orally during the Open-Label Titration Period and the Double-Blind Withdrawal Period: • 80 mg/day SDX, orally • 160 mg/day SDX, orally • 240 mg/day SDX, orally • 320 mg/day SDX, orally

<table>
<tr><td></td><td>
Placebo, orally (Withdrawal Period only)
All study drugs will be taken orally as capsules with approximately 240 mL (8 oz) water. Study drug may be taken with or without food. The capsules must be swallowed whole without cutting, crushing, chewing, or opening.
The SDX amount and the total equivalent amount of d-MPH for each daily dose, are listed in the following table:
<table>
<tr><th>SDX (mg)</th><th>SDX Cl (mg)</th><th>Equimolar d-MPH HCl dose (mg)</th></tr>
<tr><td>80</td><td>85.7</td><td>43.1</td></tr>
<tr><td>160</td><td>171.3</td><td>86.2</td></tr>
<tr><td>240</td><td>257.0</td><td>129.4</td></tr>
<tr><td>320</td><td>342.7</td><td>172.5</td></tr>
</table>
Subjects will complete a dosing diary starting after the administration of the first dose of study drug (evening of Visit 2) until the last administration of study drug (in the evening or morning before Visit 8).
</td></tr>
<tr><td>PROHIBITED MEDICATIONS</td><td>
Medications to treat IH and all medications that can affect wakefulness and sleep are prohibited during the trial, including the following:

Wake-Promoting Agents (WPAs)
CNS Stimulants.
CNS sedating and/or anti-insomnia agents: oxybates, benzodiazepine hypnotics (BZRAs), nonbenzodiazepine BZRAs, orexin receptor antagonist insomnia treatments, sedating anxiolytics, sedating antidepressants, sedative antihistamines, neuroleptics, opioids, barbiturates. gamma-hydroxybutyrate (GHB, oxybate) dehydrogenase inhibitors, dopamine antagonist antiemetics, melatonin and melatonin receptor agonists, clonidine, myorelaxants/antispasmodics. and any other medication that may cause sedation.

The following medications are also prohibited with methylphenidate treatment due to possible pharmacodynamic drug-drug interactions: monoamine oxidase inhibitors (MAOIs), neuroleptics, coumarin anticoagulants, anticonvulsants, halogenated anesthetics, antihypertensive drugs, and phenylbutazone.

Examples of prohibited medications are listed in Section 10.

If a subject has received any of the therapies listed above, a washout-period of at least 14 days, or equivalent to 5 half-lives of the drug, whichever is longer (and at least 30 days for
</td></tr>
</table>

	sedating antidepressants; 14 days for CNS stimulants), is required prior to the first dose of study drug. Subjects must abstain from these medications during the study until the Follow-Up Phone Call or Early Termination. Patients may be switched from a sedating to a non-sedating antidepressant as long as the switch occurs at least 14 days before Visit 2.
EFFICACY EVALUATION TOOLS	The following scales will be used during the Open-Label Titration Period and the Double-Blind Withdrawal Period: • Epworth Sleepiness Scale (ESS) (Johns 1991): Validated questionnaire to assess Excessive Daytime Sleepiness (EDS), consisting of 8 questions rated on a 4-point scale (0-3 corresponding to never, slight change, moderate chance, and high chance), indicating the usual chance of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher the subject's average daytime sleepiness. There is a risk of pathological daytime sleepiness if the score is >10. • Brain Fog Scale: (Ross 2013): A questionnaire of 19 scaled questions (scale from 0 to 4) that evaluate frequency, severity, descriptors, and triggers of brain fog (strongly agree, agree, neutral, disagree, and strongly disagree). Severity of brain fog is rated on a scale from 0 to 100 in 10-point intervals with higher numbers indicating increased severity. "Brain Fog" or cognitive impairment is a term used for certain symptoms that can affect the ability to think and function, including a lack of mental clarity; and a feeling of being mentally sluggish and fuzzy, leading to forgetfulness, mental cloudiness, and difficulty focusing, thinking and communicating. Other symptoms include thoughts moving too quickly, detached, lost, and sleepy. • Clinical Global Impression of Severity (CGI-S) (Guy 1976; Busner and Targum 2007) The CGI-S is a clinician-rated scale based on the response to 1 question that evaluates the severity of symptoms in the study on a scale from 1 (normal, not at all ill) to 7 (among the most severely ill patients). • Patient Global Impression of Severity (PGI-S) (adapted to IH from Viktrup 2012 and Martinez-Martin 2015) The PGI-S is a single-item patient-rated questionnaire of hypersomnia severity ("How would you describe your hypersomnia over the past week?"), with one of

	6 possible responses: 0 (none), 1 (very mild), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe). • IH Severity Scale (IHSS) (Dauvilliers 2019): The scale measures severity of both nighttime and daytime IH symptoms and sleep inertia (or "sleep drunkenness") related to each, as well as impaired daytime functioning. Patients rate severity and frequency in 17 questions using a 4- or 5-point scale for each question. The total score will range from 0 to 50. A score of 22 or below is typical for people without any sleep disorder. Higher scores on the IHSS indicate more severe symptoms of IH. • Modified Karolinska Sleepiness Scale (Mod-KSS) (Akerstedt 1990) is a 10-point scale used to measure at-the-moment (during first hour after awakening) sleepiness. Scores range from 1 to 10 (1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy – but no difficulty remaining awake, and 9 = extremely sleepy – fighting sleep, and an additional score for the modified version: 10 = extremely sleepy, falls asleep all the time). Scores on the Mod-KSS increase with longer periods of wakefulness. On this scale, subjects will indicate daily which level best reflects their sleepiness experienced during the first hour after awakening and from 5 pm to 6 pm, from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. • PROMIS®-29 Scales: Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Scale, Hays 2018). PROMIS® is a NIH initiative to develop state-of-the-science self-report measures to assess functioning and well-being in physical, mental, and social domains of health (Cella 2010). Each question is rated on a scale from 1 to 5 corresponding with "Not at all", "A little bit". "Somewhat", "Quite a bit", and "Very much", or "Very Poor", "Poor", "Fair", "Good", and "Very Good", depending on the question. Domains used in the study will include Fatigue, Ability to Participate in Social Roles and Activities, and Depression. • Patient-Reported Wakefulness Questionnaire (ZOGIM-A) (Shapiro 2006): The scale evaluates a patient's experiences with alertness over the course of the day, querying the subjective impact of environmental factors (eg, caffeine, exercise), the anticipated benefits of increased energy levels, and the perceived proportion of the day spent at high levels of alertness. Ten items are

	scored using a 5-point scale ranging from 1 ("Extremely") to 5 ("Not at all"). Summing the scores obtained on each item provides a global index – lower scores denote impaired alertness while higher scores indicate high alertness. • Sleep Inertia Visual Analog Scale (SIVAS): At-the-moment VAS to assess difficulty of waking up in the morning. Subjects will complete the SIVAS daily at approximately 1 hour after awakening from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. • Sleep Diary: Subjects will keep a Sleep Diary on a day-by-day basis (reflecting a subjective global appraisal of each night and daytime sleep) to collect self-reported time-in-bed, sleep duration, sleep onset latency, night awakenings, sleep quality, number and duration of daily naps, etc. Subjects will complete the Sleep Diary daily from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit.
SAFETY ASSESSMENTS	• The occurrence of Adverse Events (AEs) will be assessed following enrollment (signing of consent) and ending with the Follow-Up Phone Call or Early Termination. AEs will be classified as Treatment-Emergent AEs (TEAEs) when they occurred after administration of the first dose of study drug. • Physical examinations will be performed at Screening, before the first dose of study drug (Visit 2), and at the end of the Withdrawal Period (Visit 8) or at the Early Termination Visit. All or part of a physical examination can be performed for investigation of a possible or established Adverse Event. • Clinical laboratory tests (chemistry, hematology, and urinalysis) will be performed at Screening and at the end of the Withdrawal Period (Visit 8) or at the Early Termination Visit. • ECG parameters will be collected at Screening, before the first dose of study drug (Visit 2), and at all other visits of the Titration Period and the Withdrawal Period (Visits 3-8), and at the Early Termination Visit. • Vital signs will be collected at Screening, before the first dose of study drug (Visit 2), and at all other visits of the Titration Period and the Withdrawal Period (Visits 3-8), and at the Early Termination Visit . • Body weight will be measured at Screening, before the first dose of study drug (Visit 2), and at all other visits of the Titration Period and the Withdrawal Period (Visits 3-8), and at the Early Termination Visit. • C-SSRS "Baseline/Screening" version will be assessed at Screening, and "Since Last Visit" version will be assessed at

	Visit 2-8 and the Early Termination Visit. • Sleep quality will be rated using question #6 of the Pittsburgh Sleep Quality Index (PSQI-Q6) before the first dose of study drug (Visit 2), and at Visits 5, 7, and 8 of the Titration Period and the Withdrawal Period, and at the Early Termination Visit.
EFFICACY ASSESSMENTS	• Efficacy assessments made at the research sites will be performed before the first dose of study drug (Visit 2) and at all visits of the Titration Period and the Withdrawal Period (Visits 3-8). The ESS will also be performed at Screening. • Efficacy assessments based on forms or questionnaires while subjects are at home (SIVAS, Mod-KSS and Sleep Diary) will be performed daily from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit.
PHARMACOKINETIC SAMPLING	At least 12 subjects in each treatment regimen group (24 subjects in total) will visit the study site for a PK Visit, and will stay for a minimum of 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples. This PK Visit may coincide with Visit 6 or may occur at a separate visit after Visit 5 and before Visit 7. See Section 1.1 for the Schedule of Events during the PK Visit, including dose administration and PK blood sampling times.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will participate in the study as outpatients for up to 94 days, a screening period up to 35 days , a 35-day Open-Label Titration Period, a 14-day Double-Blind Withdrawal Period and a Follow-Up Phone Call 7 ±3 days after the administration of the last dose of the Double-Blind Withdrawal Period. If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, then sites will be instructed to collect data for select safety assessments (vital signs, weight, ECG, clinical laboratory tests, physical examinations, C-SSRS) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit.
SAFETY ENDPOINTS	The Primary Endpoint is the safety and tolerability based on the following assessments: The occurrence of Treatment-Emergent Adverse Events (TEAEs), physical examinations, clinical laboratory tests (chemistry, hematology, and urinalysis), ECGs, vital signs, body weight, C-SSRS, and PSQI-Q6.
EFFICACY ENDPOINTS	Secondary Endpoints (Efficacy) will be assessed as the change from baseline of the following assessment scores during the Double-Blind Withdrawal Period (Visit 7 to Visit 8):

	• Excessive Daytime Sleepiness (EDS) assessed with the Epworth Sleepiness Scale (ESS).
	• "Brain Fog" (Brain Fog Scale)
	• Clinical Global Impression of Severity (CGI-S) score
	• Patient Global Impression of Severity (PGI-S) score
	• IH Severity Scale (IHSS) Total Score (median).
	• Morning and later afternoon sleepiness (Mod-KSS score)
	• Selected domains of PROMIS®-29:
	  ○ Fatigue
	  ○ Social Functioning (Ability to Participate in Social Roles and Activities)
	  ○ Depression
	• Patient-reported wakefulness (ZOGIM-A score)
	• SIVAS
	• Data collected/calculated from the Sleep Diary (including Total Sleep Time and Total Nap Time).
	The primary efficacy endpoint is the change in ESS from Visit 7 to Visit 8.
	All retrospective efficacy endpoints (all efficacy endpoints except at-the-moment SIVAS and Mod-KSS) will be assessed with a look-back period of 1 week.
	All efficacy endpoints will also be analyzed during the visits of the Open-Label Titration Period (Visit 2 to each of Visits 3-7).

PHARMACOKINETIC ENDPOINTS	The following key steady-state PK parameters will be calculated for SDX, d-MPH, and ritalinic acid, in subjects with adequate PK data: $AUC_{0\text{-}24h,ss}$, $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$. For the bid regimen, applicable PK parameters will be calculated separately for the pm and am doses.
SAMPLE SIZE CALCULATION	Since this is an exploratory study to determine the effect size, dose range and best dosing regimen of SDX for the treatment of IH, no formal sample size calculations were performed. However, the chosen sample size would be powered at 80% to detect an effect size of 1.2; a study of a wake-promoting agent in narcolepsy achieved an effect size of approximately 1.0 on the ESS (Watson 2021). A second study of a CNS sedating agent (Sodium oxybate) in IH achieved an effect size of 1.6 on the ESS (Dauvilliers 2021). In both cases, the standard deviation of the difference between active and placebo for ESS was approximately 4.0. This standard deviation would yield a confidence interval of ±3.2 around the two placebo/active comparisons in this study. A non-binding interim analysis following the exit from the study of the first 50% of randomized subjects will evaluate the conditional power and potentially increase the sample size.

INTERIM ANALYSIS	An interim analysis based on the change from the end of the Open-Label Titration Period to the end of the Double-Blind Withdrawal Period in ESS is planned once the first 50% (24 patients) of the initially planned sample size have completed or discontinued from the study. This will be completed independently within each regimen to determine whether an increase in sample size is recommended for that regimen. An unblinded team, isolated from all study operations, will perform the analysis and return a recommended sample size increase; any increase will be capped at 12 additional subjects in each regimen (4 placebo and 8 active in each of the qd pm and bid dosing regimens). Other than the recommendation, the Sponsor will remain blinded to the interim results as well as individual subject assignments. Final p-values will be adjusted using the Cui, Hung, Wang approach (Cui 1999). Full details will be provided in an Interim Analysis Charter and the Statistical Analysis Plan.
ANALYSIS POPULATIONS	• **Safety Population:** All enrolled subjects who received at least one dose of study drug and who have at least one post-dose safety assessment. Safety measures will be analyzed for all subjects in the Titration Period by dosing regimen. Demographics and baseline characteristics will be summarized for this population when describing all subjects treated. • **Withdrawal Safety Population:** All subjects randomized to a treatment in the Double-Blind Withdrawal Period who received at least one dose of study drug in that period and who have at least one post-dose safety assessment in the Double-Blind Withdrawal Period. Safety measures will be analyzed for subjects in the Withdrawal Period by treatment and regimen (and pooled across regimen). Demographics and baseline characteristics will be summarized for this population when describing subjects entered into the randomized withdrawal period. • **PK Population:** All subjects who provided adequate PK samples to calculate the steady-state plasma exposure of d-MPH and who do not have major protocol deviations that could potentially affect the PK conclusions of the study. Data from the PK Population will be used for PK data listings and PK analyses. Efficacy analyses will be conducted in the following populations: • **Titration Modified Intent-to-Treat (MITT) Population:** All subjects in the Titration Period who

	received at least one dose of study medication and have at least one post-randomization ESS score in the Titration Period. Demographics and titration baseline characteristics will be summarized for the Titration MITT Population. • **Withdrawal MITT Population**: All randomized subjects in the Withdrawal Period who received at least one dose of study medication and have at least one post-randomization ESS score in the Withdrawal Period. Demographics and randomization baseline characteristics will be summarized for the Withdrawal MITT Population.
STATISTICAL SAFETY ANALYSES	The occurrence of Treatment-Emergent Adverse Events (TEAEs) will be assessed following enrollment (signing of consent) and ending with the Follow-Up Phone Call or Early Termination. Additional safety evaluations will include physical examinations, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, body weight, and C-SSRS assessed at each study visit, and PSQI-Q6 assessed at selected visits. Safety analyses will be performed by descriptive statistics, without formal statistical testing (except for PSQI-Q6). Safety analyses will be reported separately for the Titration Period and the Double-Blind Withdrawal Period using the respective safety populations for each. Reporting will be by regimen in the titration period and by treatment and regimen in the double-blind period.. PSQI-Q6 scores will be analyzed similarly to the continuous efficacy endpoints. Subgroup analyses for safety will be performed by gender.
STATISTICAL EFFICACY ANALYSES	Descriptive Statistics: Changes from titration and randomization baseline of all efficacy assessments at each subsequent visit will be summarized descriptively. Categorical responses to efficacy questionnaires will be summarized by the number and percentage of subjects who selected each response. Comparisons between treatments will be conducted for each dosing regimen. Other comparisons may include an analysis with data pooled from both dosing regimens and a direct comparison of both dosing regimens. All statistical tests will be for information purposes only.

	Primary efficacy analysis: change in a subject's ESS score in the Withdrawal MITT Population at the end of the Withdrawal Period (Visit 8) compared to the randomization baseline at the start of the Withdrawal Period (Visit 7). The primary efficacy evaluation will be based on the difference (SDX minus placebo) for each regimen in least squares mean estimates of the change from the randomization baseline score, obtained from an ANCOVA that includes randomization baseline ESS, treatment (active or placebo), regimen (bid or qd), and treatment by regimen as covariates. Continuous additional efficacy endpoints, if appropriate, will be analyzed with the same analysis method as the main analysis. For the analyses in the Titration Period, the titration baseline (Visit 2) will be used for calculating the change from baseline. Analysis of the change in CGI-S and PGI-S responders from baseline to each post-baseline visit will be evaluated at each post-baseline visit within each treatment group using the Pearson chi-square test (equivalent to the difference in proportions z-test). Subgroup analyses for efficacy will be performed by gender, in subjects with and without long sleep times, in subjects with and without sleep inertia, and in subjects with and without brain fog. A long sleep time is defined as a TST >10 hours based on the Sleep Diary during the last 10 days prior to Visit 2. Subjects with sleep inertia will be identified based on the titration baseline IHSS (Visit 2). Subjects with Brain Fog will be identified based on the titration baseline Brain Fog Scale (Visit 2). Details will be provided in the SAP.
STUDY PROCEDURES	The study procedures are outlined in the Schedule of Events (Section 1).

1. SCHEDULE OF EVENTS

ASSESSMENTS	SCREEING PERIOD		OPEN-LABEL TITRATION PERIOD Days 1-35(5 Weeks)					DOUBLE-BLIND WITHDRAWAL PERIOD Days 35-49 (14 Days)		ET [29] (EOS)	FOLLOW-UP PHONE CALL 7 Days
Study Visit Day [30]	-35	-11 (±2)	1	7 (±3 days)	14 (±3 days)	21 (±3 days)	28 (±3 days)	35 (±3 days)	49 (EOT) (±3 days)	-	56 (±3 days)
Visit Number	1	1A	2	3	4	5	6	7	8		-
Informed Consent	X										
Inclusion/Exclusion	X	X	X	X	X	X	X	X	X		
Demographics	X										
Medical History	X		X								
IH Diagnosis (ICSD-3) [1]	X										
Physical Examination [2]	X		X						X	X	
Body Weight, Height, and BMI [3]	X		X	X	X	X	X	X	X	X	
Vital Signs [4]	X		X	X	X	X	X	X	X	X	
12-Lead ECG [5]	X		X	X	X	X	X	X	X	X	
Chemistry/ Hematology/Urinalysis	X		X						X	X	
Test for Alcohol/Drugs of Abuse [6]	X		X								
Pregnancy Test [7]	X		X	X	X	X	X	X	X	X	
C-SSRS [8]	X		X	X	X	X	X	X	X	X	
Washout Meds	X										
Randomizations [9]			X					X			
Dosing [10]			X	X	X	X	X	X	X		
Dosing Diary [11]		X	X	X	X	X	X	X	X		
Drug accountability & compliance assessment [12]				X	X	X	X	X	X		
Dispense Study Drug			X	X	X	X	X	X			
Pharmacokinetics [13]							X				
ESS [14]	X		X	X	X	X	X	X	X		
Brain Fog Scale [15]			X	X	X	X	X	X	X		
CGI-S [16]			X	X	X	X	X	X	X		

ASSESSMENTS	SCREEING PERIOD		OPEN-LABEL TITRATION PERIOD Days 1-35(5 Weeks)					DOUBLE-BLIND WITHDRAWAL PERIOD Days 35-49 (14 Days)		ET [29] (EOS)	FOLLOW-UP PHONE CALL 7 Days
Study Visit Day [30]	-35	-11 (±2)	1	7 (±3 days)	14 (±3 days)	21 (±3 days)	28 (±3 days)	35 (±3 days)	49 (EOT) (±3 days)	-	56 (±3 days)
Visit Number	1	1A	2	3	4	5	6	7	8		-
PGI-S [17]			X	X	X	X	X	X	X		
IHSS [18]			X	X	X	X	X	X	X		
Mod-KSS [19]		X	X	X	X	X	X	X	X	X	
PROMIS®-29 Fatigue [20]			X	X	X	X	X	X	X		
PROMIS®-29 Social Functioning [21]			X	X	X	X	X	X	X		
PROMIS®-29 Depression [22]			X	X	X	X	X	X	X		
ZOGIM-A [23]			X	X	X	X	X	X	X		
SIVAS [24]		X	X	X	X	X	X	X	X	X	
Sleep Diary [25]		X	X	X	X	X	X	X	X	X	
PSQI-Q6 [26]			X			X		X	X	X	
Adverse Events [27]			X	X	X	X	X	X	X	X	X
Concomitant Medications [28]	X		X	X	X	X	X	X	X	X	X

EOS = End of Study; EOT = End of Treatment; ET = Early Termination; ECG = Electrocardiogram; MPH = methylphenidate; see footnotes for other abbreviations.

1. IH ICSD-3: At screening, an IH diagnosis according to the International Classification of Sleep Disorders ICSD-3 criteria. Idiopathic Hypersomnia (IH) diagnosis and confirmation will be done according to the International Classification of Sleep Disorders ICSD-3 criteria. If documentation of IH diagnosis is unavailable in the screening window, diagnostic testing must be performed according to ICSD-3 criteria. This may include one of the following to confirm the diagnosis of IH:
   - Nocturnal polysomnogram (PSG) followed by a multiple sleep latency test (MSLT). The duration of the MSLT must be long enough to include at least 4 naps.
   - 24-hour PSG
   - Wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).
2. Complete physical examination at Screening, Visit 2, Visit 8, and at the ET visit (if possible).
3. Body Weight, Height, and BMI: The measurement of body weight will be obtained at Screening, at Visits 2-8, and at the ET visit (if possible). Height and BMI will be obtained at the Screening visit only.
4. Vital Signs: Vital sign measurements will be obtained after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least

2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded. Vital signs will include blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Vital signs will be obtained at Screening, Visits 2-8, and at the ET visit (if possible).

5. Electrocardiogram (ECG): A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded. ECGs will be obtained at Screening, at Visits 2-8, and at the ET visit (if possible).
6. Urine screen or breath test for alcohol and urine screen for drugs of abuse: Urine or breath will be tested for alcohol, and urine will be tested for drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone) and methylphenidate at Screening (Visit 1) and at Visit 2. A urine dipstick will be used to screen for the presence of MPH in the urine. Subjects with a positive urine drug screen (eg, amphetamines, methylphenidate) may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required (test at Visit 2 needs to be negative). Subjects with a positive test at Screening may be rescreened (test at Visit 2 needs to be negative).
7. Pregnancy Test: Pregnancy tests will be performed for all female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at Screening and at Visit 8. A urine pregnancy test will be performed at Visits 2-7, and at the Early Termination Visit. A positive pregnancy test before Visit 8 will exclude a subject from further participation into the study.
8. Columbia Suicide Severity Rating Scale (C-SSRS, Appendix O): The "Baseline/Screening" version will be assessed at Screening, and the "Since Last Visit" version will be assessed at all other visits (Visits 2-8, and ET, if possible).
9. **Randomizations:** There will 2 different randomizations in the study, as follows;
   Open-Label Titration Period (Visit 2 to Visit 7): The subjects will be randomized at Visit 2 to one of the following 2 dosing regimens (non-blinded randomization):
   Treatment X: once daily at night (qd pm)
   Treatment Y: half the daily dose in the morning and at night (bid)
   This randomization will be stratified by gender.
   Subjects will attend weekly clinic visits for a period of 5 weeks in the Titration Period. The subject's treatment will be titrated (change of dose as needed) to an optimal daily dose of SDX starting with the lowest dose, based on individual tolerability and effect. The 4 possible SDX doses to be taken orally are:
   - 80 mg/day SDX
   - 160 mg/day SDX
   - 240 mg/day SDX
   - 320 mg/day SDX

   Double-Blind Withdrawal Period (Visit 7 to Visit 8): will consist of 2 weeks during which the subjects will receive the optimized dose. The subjects will have clinic visits at the beginning and end of the period.
   At the start of the Withdrawal Period (Visit 7), subjects within each treatment group of the Titration Period will be randomized in a 2:1 ratio to SDX or placebo.
   - Subjects receiving Treatment X in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period (blinded randomization):
     Treatment A: SDX, once daily at night (qd pm)
     Treatment B: Placebo, once daily at night (qd pm).
   - Subjects receiving Treatment Y in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period (blinded randomization):

Treatment C: SDX, half the daily dose in the morning and at night (bid)
Treatment D: Placebo, half the daily dose in the morning and at night (bid)

This randomization will be stratified by the optimized dose. Subjects will keep taking study drug qd pm or bid (pm and am) as assigned by the randomization at the start of the Titration Period.

10. Dosing: All study drugs will be taken orally as capsules with approximately 240 mL (8 oz) water. Study drug may be taken with or without food. The capsules must be swallowed whole without cutting, crushing, chewing, or opening. Time of dosing and whether a meal (excluding small snacks such a candy bar) was consumed ±1 hour of dosing will be recorded daily or twice daily in the Dosing Diary.
    The following daily doses of study drug will be administered orally during the Open-Label Titration Period and the Double-Blind Withdrawal Period:
    - 80 mg/day SDX, orally
    - 160 mg/day SDX, orally
    - 240 mg/day SDX, orally
    - 320 mg/day SDX, orally
    - Placebo, orally (Withdrawal Period only)
11. Dosing Diary: Subjects will complete the Dosing Diary on a day-to-day basis after taking each dose of study drug (once or twice per day) starting after the administration of the first dose of study drug (evening of Visit 2) until the last administration of study drug (in the evening or morning before Visit 8), or Early Termination. The subjects will be trained on the use at Visit 1A.
12. Drug Accountability & Compliance Assessment: All study drug will be recorded by each site's pharmacy staff member or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site at each visit for subjects receiving study drug since the previous visit.
13. Pharmacokinetics: Subjects will visit the study site and will stay for a minimum of 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples. This PK Visit may coincide with Visit 6 or may occur at a separate visit after Visit 5 and before Visit 7. See Section 1.1 for the Schedule of Events during the PK Visit.
14. Epworth Sleepiness Scale (ESS): will be obtained at Screening and Visits 2-8.
15. Brain Fog Scale: will be obtained will be obtained at Visits 2-8.
16. Clinical Global Impression of Severity (CGI-S): will be obtained at Visits 2-8.
17. Patient Global Impression of Severity (PGI-S): will be obtained at Visits 2-8.
18. IH Severity Scale (IHSS): will be obtained at Visits 2-8.
19. Modified Karolinska Sleepiness Scale (Mod-KSS): Subjects will complete the Mod-KSS form on a day-by-day basis at approximately 1 hour after awakening and at approximately 6 pm, starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. The subjects will be trained on the use at Visit 1A.
20. Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Fatigue): will be obtained at Visits 2-8.
21. Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Social Functioning): will be obtained at Visits 2-8.
22. Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Depression): will be obtained at Visits 2-8.
23. Patient-Reported Wakefulness Questionnaire (ZOGIM-A): will be obtained at Visits 2-8.
24. Sleep Inertia Visual Analog Scale (SIVAS) to assess difficulty of waking up in the morning. Subjects will complete the SIVAS on a day-by-day basis at approximately 1 hour after awakening starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. The subjects will be trained on the use at Visit 1A.
25. Sleep Diary: Subjects will keep a sleep diary on a day-by-day basis starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. The sleep diary should be completed within one hour

after awakening in the morning, and again at night before going to sleep. The subjects will be trained on the use at Visit 1A.

26. Patient-reported sleep quality scores of question #6 of the Pittsburgh Sleep Quality Index (PSQI-Q6) will be obtained at Visits 2, 5, 7, and 8, and at the Early Termination Visit.
27. Adverse Events: will be assessed and recorded in the eCRF from Visit 2 through either the Follow-Up Phone Call or at the Early Termination Visit.
28. Concomitant Medications: new and/or changed medications and dose, medical treatments and/or therapies will be recorded at Screening through either Follow-Up Phone Call or at the Early Termination Visit.
29. Early Termination (ET): is defined as withdrawal after at least 1 dose of study drug administered in either the Open-Label Titration Period or the Double-Blind Withdrawal Period. At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the procedures of another visit, do not need to be repeated. The ET procedures are not required for subjects who screen fail before the administration of their first dose of study drug. Subjects who withdraw early from the study and complete the above ET procedures will not have a Follow-Up Phone Call. Therefore, the ET Visit is the EOS for these subjects.
30. Assessment Changes due to COVID-19: If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, then sites will be instructed to collect data for select safety assessments (vital signs, weight, ECG, clinical laboratory tests, physical examinations, C-SSRS) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit. These assessments will be mapped to the nearest scheduled visit. Changes in scheduled visits and corresponding assessments due to COVID-19 restrictions will be captured in the eCRF. Assessments that do not require the subject's presence at the site will be collected by phone at the scheduled visit times. If needed, alternate measures to dispense study drug to the subjects during their COVID-19 isolation period will be implemented (eg, study drug directly delivered to the subject's residence or dispensed to another family member).

1.1. Schedule of Events for Pharmacokinetic Sample Collections (PK Visit)

Procedures (in sequence)	PK Visit (after Visit 5 and before Visit 7) [2, 3]	
	Time of Procedure	
	Treatment X (SDX qd pm)	Treatment Y (SDX bid) [2]
Reminder Call for PK Visit [1]	3-4 days before PK Visit	
Admission [2]	✓	
Non-PK Study Procedures [3]	✓	
Dosing Diary Review/Plan Bedtime and Wake-Up Times/Plan Mealtimes [4]	✓	
0-h (predose) sample	Within 10 min before PM dose	
PM Dose Administration [5]	0 h (just before going to sleep)	
Going to sleep [6]	✓	
Nighttime PK sampling [7]	1, 2, 4, 5, 6, 8, 10, 12 h after PM dose	1, 2, 4, 5, 6, 8, 10, 12 h [10] after PM dose
Awakening [8]	✓	
0-h (predose) sample	-	Within 10 min before AM dose (shortly after awakening)
AM Dose Administration [9]	-	0 h
Daytime PK sampling	16, 24 h after PM dose	1, 2, 4, 5, 6, 8, 10, 12 h [11] after AM dose
Last PK sampling	24 h after PM dose	24 h ***after PM dose***
Dismissal	✓	

The blood samples for PK will be collected at the nominal time points ±5 minutes for sampling times 1-10 hours postdose and ±10 minutes time points after 10 hours postdose; and within 10 minute of dosing for the predose (0 hour) samples.

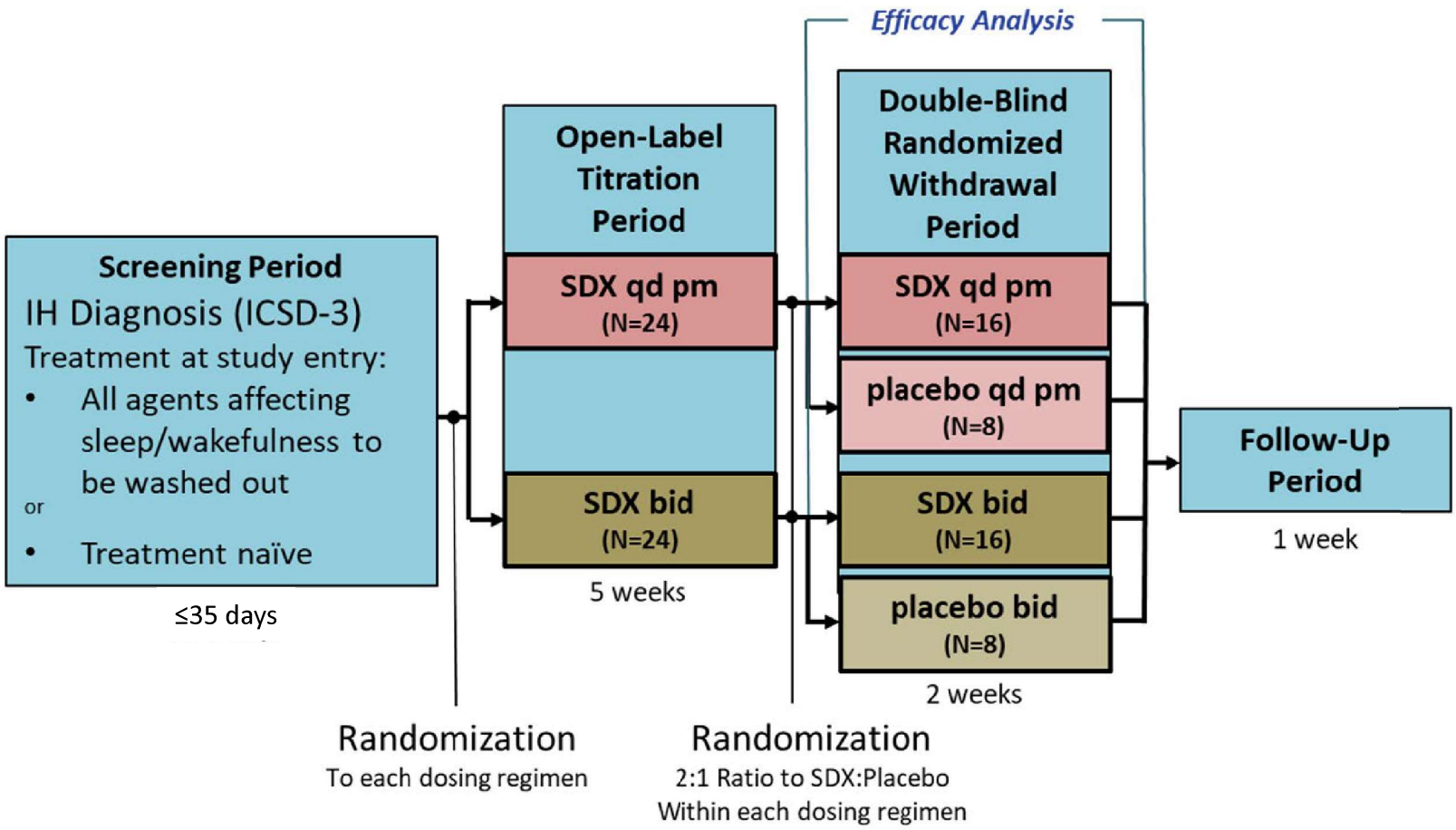
1. Site staff will monitor whether subjects have completed the Dosing Diary during the 3 days before the scheduled PK Visit, and contact the subjects if needed.
2. Subjects will be admitted to the study site to stay for a minimum of 1 night and day for dosing and the collection of blood samples for PK over a 24-hour period. This PK Visit may coincide with Visit 6 or may occur at a separate day after Visit 5 and before Visit 7. Subjects will need to have received the same daily dose of study drug for at least 3 consecutive days immediately before the PK Visit.
3. If the PK Visit coincided with Visit 6, the Visit 6 procedures will be conducted before starting the PK-related procedures; if the PK Visit is on a separate day between the Visit 5 and Visit 7 day, the following procedures will be conducted before starting the PK-related procedures:
   a. Record remaining study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused (remaining) medication to the clinical site. Subjects will keep the remaining study drug, as appropriate (since they will continue at-home dosing after the PK Visit).
   b. Vital signs after a minimum of 3 minutes of ret (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
   c. Assessment and review of AEs.
   d. Review of concomitant medications, treatment and/or therapies since last visit.
   e. Confirm that subjects are completing the Sleep Diary, SIVAS and Mod-KSS daily.
   f. Confirm scheduling of the next scheduled visit.

4. The Dosing Diary will be reviewed by site staff during the PK Visit. Based on review of the PK Diary with the subject, the following will be predetermined for the PK Visit: bedtime and time of awakening, mealtimes, and times of dose administration will be as close as possible to the subject's usual times. Actual bedtime and wake-up time, mealtimes, and times of dose administration, as well as the dose size will be recorded.
5. Subjects receiving the bid regimen will take the AM dose at home, before visiting the study site for the PK Visit. The PM dose will be administered at the study site. While at the study site, doses will be administered under the supervision of site staff, and dosing times will be recorded. If possible, the dose size administered will be same dose size that the subject has taken during the last 3 days before the PK Visit. This dose is not necessarily the optimal dose.
6. Time of going to sleep for the night during the PK Visit will be as close as possible to a subject's regular time of going to sleep for the night.
7. Samples collected during the night (after the pm dose) will be collected under "sleep conditions" including the following: subjects will need to lay down all night except for bathroom visits, dim lights, quiet environment (no loud noises, no use of electronics, TV, etc) to mimic night conditions as much as possible
8. Time of awaking during the PK Visit will be as close as possible to a subject's regular time of awakening; if subject wakes up earlier, subject will stay in bed until the predetermined time of awakening; if subject is still asleep, site staff will wake up the subject.
9. Subjects receiving the bid regimen will take the AM dose in the morning after the PK day at the study site under the supervision of site staff. Dosing times will be recorded.

NOTE: Since the bid regimen may be different for different subjects, with the dosing interval between the pm and am doses different from 12 hours, the PK sampling times will need to be adjusted accordingly, as explained in the following footnotes:

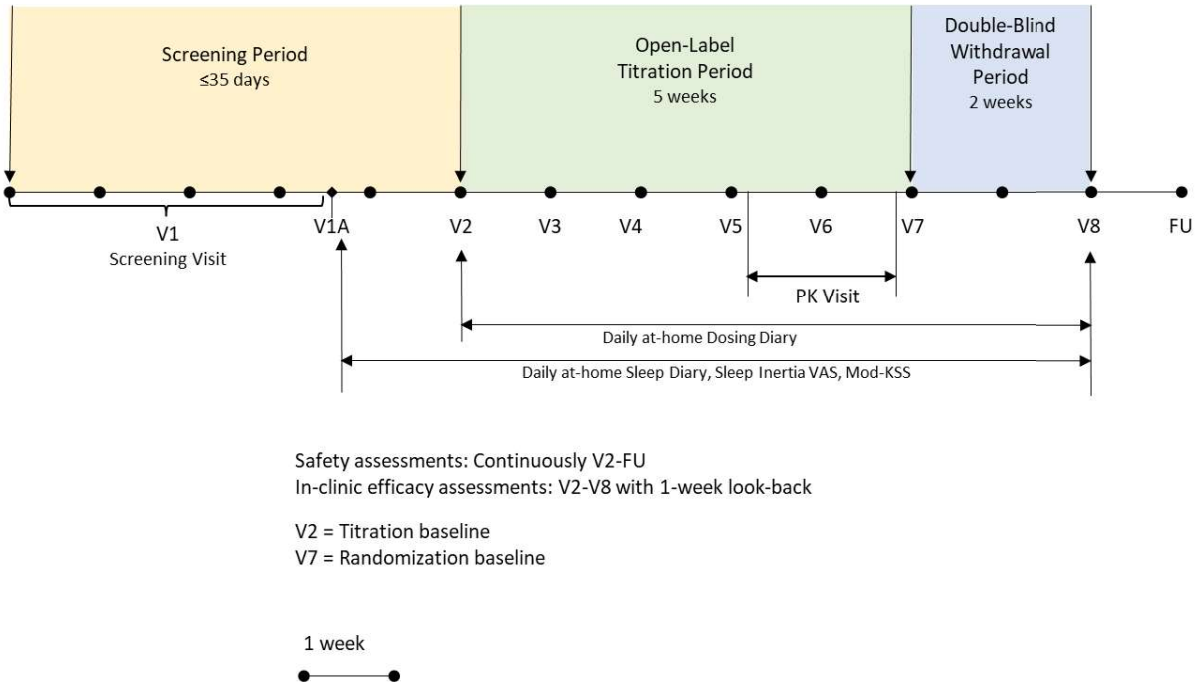
10. Treatment Y (bid regimen): The duration of the nighttime dosing interval is determined by the subject's usual total time asleep which may be shorter than 12 hours. Therefore, If the later sampling time(s) (eg, 12 h sample) after the pm dose fall at a time earlier than 10 minutes before the am dose predose sample, this sample will not be collected.
11. Treatment Y (bid regimen): The duration of the daytime dosing interval is determined by the subject's usual total time awake, which may be shorter than 12 hours. Therefore, If the later sampling time(s) (eg, 12 h sample) after the am dose fall at a time earlier than 10 minutes before the 24-hour sample (24 hours after the pm dose), this sample will not be collected.

2. STUDY DESIGN SCHEMATIC



IH = Idiopathic Hypersomnia; SDX = Serdexmethylphenidate;
ICSD-3 = The International Classification of Sleep Disorders – Third Edition

2.1. Study Design Schematic by Visit



V = Visit; FU = Follow-Up Phone Call; PK = Pharmacokinetics
VAS = Visual Analog Scale; Mod-KSS = Modified Karolinska Sleepiness Scale

3. BACKGROUND

3.1. Idiopathic Hypersomnia (IH)

Idiopathic Hypersomnia (IH) is a chronic, debilitating, central disorder of hypersomnolence (CDH). The cardinal feature of IH is excessive daytime sleepiness (EDS, aka hypersomnolence or hypersomnia), characterized by daytime lapses into sleep or an irrepressible need to sleep that persists even with adequate or prolonged nighttime sleep (AASM 2014). While EDS is reported by virtually all patients with IH, many also report sleep drunkenness (ie, severe sleep inertia) and long (>1 hour) daytime naps that are typically unrefreshing (Vernet 2010, Trotti 2020). Patients with IH also frequently complain of cognitive and attentional difficulties, poor memory, fatigue, impaired alertness, depressive symptoms, and automatic behaviors, all of which contribute to overall disease burden and impaired quality of life (Vernet 2010, Trotti 2020, Schneider 2021a, Schneider 2021b).

While there is substantial variability in estimates of the prevalence of IH, the available literature support that IH is a rare disease that is less common than narcolepsy (Billiard and Dauvilliers 2001, Acquavella 2020). For example, in a claims-based, retrospective cohort analysis conducted for the years 2013-2016, the US prevalence of IH in 2016 was estimated to be 10.3 per 100,000 persons (Acquavella 2020). Using population data from the last official US census (April 2020), there were approximately 331,450,000 US citizens. It is therefore estimated that approximately 34,000 individuals in the United States suffer from IH. The disease is typically diagnosed in adolescence and is usually a life-long condition, although hypersomnia has been observed to spontaneously remit in 14-25% of patients (Anderson 2007, Billiard 1996, Bruck and Parkes 1996). IH appears to be somewhat more common in females than males (Ali 2009, Billiard and Sonka 2016) although dedicated epidemiological studies are lacking.

Since there have not been any FDA approved products for the treatment of IH prior to 2021, excessive daytime sleepiness in patients with IH has historically been treated with the off-label use of alerting agents, primarily conventional stimulants such as amphetamine and methylphenidate, and the wake-promoting agents, modafinil and armodafinil (Anderson 2007, Ali 2009, Thakrar 2018, Trotti 2020). A significant number of patients are prescribed more than one alerting agent (eg, modafinil plus immediate-release methylphenidate) to optimally manage their symptoms (Ali 2009, Thakrar 2018, Pascoe 2019). Improvement in EDS following treatment with alerting agents has been reported in various case series, however randomized, controlled trials have been conducted only with modafinil (Mayer 2015, Inoue 2021). A minority of patients with IH also reported off-label use of sodium oxybate (Xyrem) (Thakrar 2018, Trotti 2020). A randomized, controlled trial of a follow-on oxybate product (Xywav) demonstrated efficacy for the treatment of IH (Dauvilliers 2022), leading to its FDA approval in 2021 as the first product for the treatment of IH (Xywav US Prescribing Information 2021).

While there are different levels of evidence that alerting agents and oxybate can ameliorate EDS in

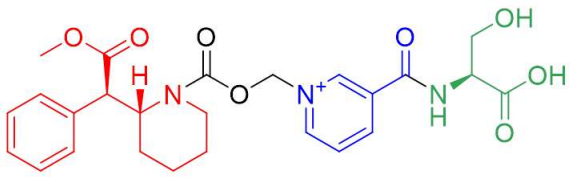
patients with IH, the response to treatment is frequently incomplete and some patients experience dose-limiting adverse effects that are typical of alerting agents and oxybate (Ali 2009, Thakrar 2018). Importantly, there is evidence that satisfaction with treatment would be enhanced if, in addition to EDS, other core symptoms (eg, cognitive impairment, brain fog) of IH were treated (Schneider 2021a, Schneider 2021b). Accordingly, there remains a need for additional efficacious treatments that can not only address EDS, but potentially other daytime symptoms associated with IH to improve the quality of life of the patients.

With respect to stimulants such as methylphenidate, the suboptimal efficacy and dose-limiting adverse effects may be due, in part, to the PK profile of specific formulations employed during treatment. For example, it is common for immediate-release methylphenidate to be administered 3-4 times per day in patients with IH (Ali 2009). The resulting PK profile is characterized by fluctuating peaks and troughs that can be associated with adverse effects and suboptimal efficacy, respectively. Similar peaks and troughs are also incorporated in the release profile of certain once-daily, extended-release methylphenidate formulations (eg, Focalin XR, Aptensio XR). The development of a methylphenidate product that sustains plasma MPH at appreciable concentrations for most of the waking day, without large exposure spikes that can be dose-limiting, may afford greater efficacy and tolerability for treating IH.

3.2. Serdexmethylphenidate (SDX) – A Prodrug of d-Methylphenidate

Zevra had identified a prodrug of d-threo-methylphenidate (aka dexmethylphenidate, d-MPH), serdexmethylphenidate (SDX) chloride, that it intends to develop for the treatment of Stimulant Use Disorder (SUD). Chemically, SDX consists of a single d-MPH molecule covalently attached via a carbamate bond to a nicotinoyl-serine moiety (Figure 1). SDX is a component of an approved product, Azstarys™ (SDX/d-MPH capsules), that was approved by the FDA in 2021, for the treatment of ADHD in patients 6 years and older.

Figure 1. SDX chemical structure



Molecular Components
red = d-methylphenidate
black = carboxymethylene linker
blue = niacin
green = L-serine

Serdexmethylphenidate (SDX)

SDX behaves as a prototypical prodrug that is devoid of pharmacological effects until metabolized to active d-MPH. The pharmacological activity of SDX, therefore, is due exclusively to its conversion to d-MPH. Upon entry to the CNS, d-MPH blocks the reuptake of dopamine and norepinephrine into presynaptic nerve terminals, thereby resulting in an enhancement of dopaminergic and noradrenergic signaling in the CNS. Because of its unique physicochemical and

pharmacokinetic properties, SDX has lower abuse potential than d-MPH HCl and has been designated a Schedule IV controlled substance.

3.3. Pharmacokinetics and Safety of Oral SDX at "High" Doses (Study KP879.101)

As part of ADHD development program, the clinical pharmacology, efficacy, and safety of SDX has been extensively studied in 16 clinical studies in which SDX Cl was administered as a single entity or in combination with d-MPH HCl. In addition, 1 study (KP879.101) was conducted in subjects with Stimulant Use Disorder (SUD). See the KP1077 Investigator's Brochure for more information.

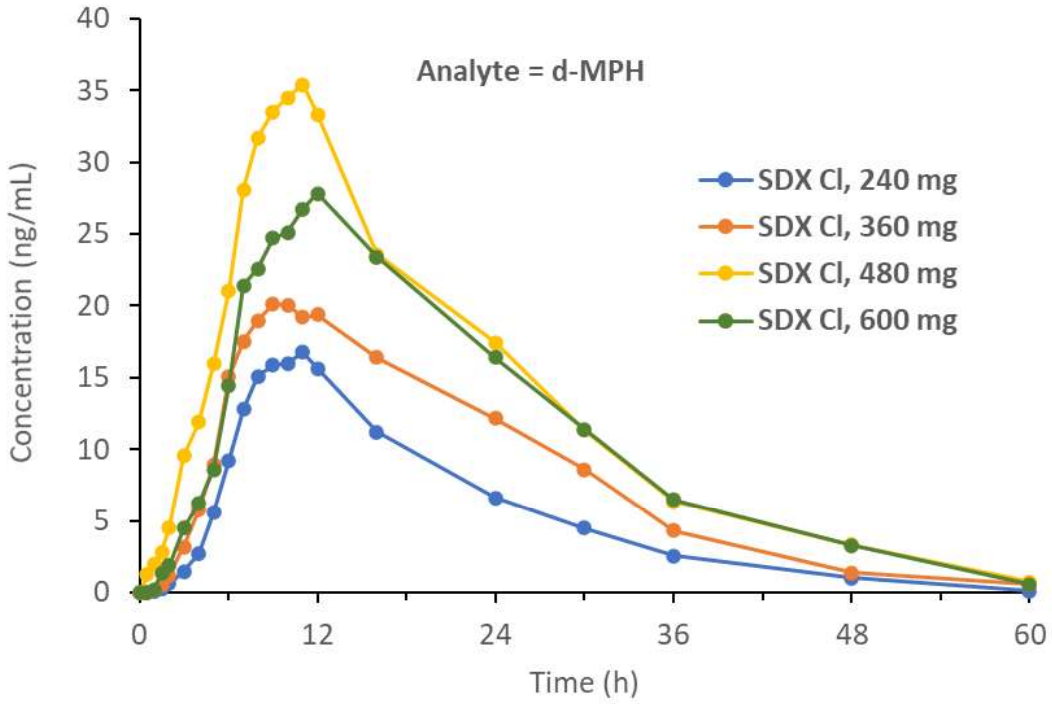
Besides the oral Human Abuse Potential (HAP) study (Study KP415.A01), wherein high doses of SDX Cl (single oral administration of 120 and 240 mg) were used in recreational stimulant users, Study KP879.101 also provided pharmacokinetic and safety data after high doses of SDX Cl. Study KP879.101 was a Phase 1, dose-escalation study to determine the pharmacokinetics and safety of single oral doses of SDX Cl (in a liquid solution) in subjects with SUD. Following screening, subjects were treated with single, ascending doses of single-entity SDX Cl (240, 360, 480, and 600 mg), with each dose separated by a minimum of 14 days.

A total of 14 subjects received at least 1 dose of SDX Cl with 14, 10, 7 and 2 subjects dosed with 240, 360, 480, and 600 mg, respectively. The mean d-MPH plasma concentrations by SDX Cl dose level (Figure 2) show a slow increase with a median T_{max} of 10-12 hours followed by a slow decline. The sustained d-MPH concentrations for an extended portion of the waking day are suitable to have a potential beneficial effect on wakefulness in patients with IH or on craving in SUD. In addition, d-MPH C_{max} and AUC increased proportionally with dose up to 480 mg SDX Cl. Since only 2 subjects received the 600 mg dose, there is insufficient data to conclude linearity up to 600 mg, although the exposure-dose relationship within each of the 2 subjects is suggestive that this is the case. The mean d-MPH plasma PK parameters by SDX Cl dose level are shown in Table 1.

Doses of 240 and 360 mg SDX Cl were well tolerated. From the 14 subjects, 11 subjects (78.6%) experienced at least 1 adverse event (AE). The most frequently reported adverse events in >2 subjects overall (>14.3% of subjects overall) by preferred term were nausea, energy increased, feeling abnormal, chills, decreased appetite, headache, hypervigilance, restlessness, euphoric mood, change in sustained attention, and hyperhidrosis, across the dose range studied (after 240 mg SDX Cl and >240 mg for most AE types); and after higher SDX doses (>240 mg SDX Cl) were sinus tachycardia (after 480-600 mg SDX Cl), electrocardiogram ST segment depression (after 480 mg SDX Cl), and insomnia (after 360-600 mg SDX Cl). Most AEs were mild or moderate in severity and were typical for CNS stimulants. There were no serious AEs (SAEs). See the KP1077 Investigator's Brochure for more details.

As a conservative approach to the safety of the subjects, only 7 and 2 of the subjects were dosed with the two highest doses (480 and 600 mg SDX Cl, respectively), because 3 subjects experienced episodes of tachycardia and/or ECG S-T depression after 480 mg SDX Cl (although they were asymptomatic) and 2 subjects experienced 24-hour insomnia after the 600 mg dose.

Figure 2. Mean d-MPH Plasma Concentration-Time Profiles After Single Oral Doses of 240. 360, 480, and 600 mg SDX Cl (Study KP879.101)



Number of subjects per SDX CL dose level:
240 mg: N=14; 360 mg: N=10; 480 mg: N=7; 600 mg: N=2.
The mean d-MPH plasma concentration-time curve for 600 mg SDX was lower than expected because only 2 subjects received this dose, and their individual exposures were the lowest compared to other subjects, even at the lower doses.

Table 1. Plasma PK Parameters of d-MPH after Single Oral Dose Administrations of 240, 360, and 480 mg SDX Cl (KP879.101).

Parameters	240 mg SDX Cl N=14	360 mg SDX Cl N=10	480 mg SDX Cl N=7
T_{max} (h)	10.0 (8.0-16.0)	11.5 (6.0-30.0)	10.0 (3.0-16.0)
C_{max} (ng/mL)	18.2 (50.6)	23.9 (42.6)	43.0 (26.9)
AUC_{24h} (h*ng/mL)	229 (51.7)	325 (38.8)	523 (20.9)
AUC_{last} (h*ng/mL)	312 (46.4)	473 (36.4)	745 (30.8)
AUC_{inf} (h*ng/mL)	317 (45.6)	481 (36.7))	760 (31.4)
CL/F (L/h)	384 (39.5)	387 (55.7)	297 (30.0)

Values are mean (CV%) except for T_{max}: median (range).
Doses in Study KP879.101 were defined in terms of the SDX salt form (240. 360, 480, and 600 mg SDX Cl); equivalent SDX doses (base form) are 224, 336, 448, and 560 mg (based molecular weights of 500.53 g/mol for SDX, and 535.98 g/mol of SDX Cl).
Since only 2 subjects received the 600 mg dose, no mean PK parameters are included for this dose.

4. STUDY RATIONALE

The current study will investigate the safety, efficacy and pharmacokinetics of SDX compared to placebo in subjects with Idiopathic Hypersomnia (IH). The study may inform about the best dosing regimen, optimal dose range, duration of treatment, and secondary endpoints for a future Phase 3 study.

4.1. Dose Rationale

The Sponsor plans to develop SDX as an oral, once- or twice-daily product (KP1077) for the treatment of IH (KP1077 program). Based on previous studies with SDX for the development in ADHD, a substantial amount of nonclinical and clinical data has been collected with this molecule (See the KP0177 Investigator's Brochure for more information). Given that pharmacodynamic responses to d-MPH are closely mirrored by plasma concentration time profiles of d-MPH (Swanson and Volkow 2003), the PK profile of SDX is informative for predicting efficacy. Mean plasma concentrations of d-MPH after single oral doses of SDX (Figure 2) begin rising at approximately 3 hours post-dose and reach a broad peak from approximately 8 to 12 hours postdose. Following the peak, there is a gradual decline in d-MPH concentrations for the remainder of the dosing interval. By producing sustained d-MPH concentrations without sharp exposure spikes, it may be possible to administer tolerable doses of SDX that are higher than immediate-release (IR) and certain extended-release (ER) formulations of MPH. Therefore, this unique PK profile provides the potential to achieve d-MPH exposure levels that can produce robust and sustained reductions in Excessive Daytime Sleepiness (EDS) in patients with IH.

In addition, dose levels of MPH products that have been used in clinical practice to treat IH or narcolepsy (a closely related sleep disorder with EDS) are informative for estimating the d-MPH exposure needed for efficacy in IH patients. Ritalin is FDA-approved for the treatment of ADHD in children and adults, and is also FDA-approved as a second-line treatment for narcolepsy in adults (Ritalin® US Prescribing Information 2021) up to 60 mg/day to increase alertness and reduce excessive sleepiness during the day. MPH products, IR Ritalin in particular, are used off-label to treat daytime sleepiness in patients with IH (Trenque 2014) and at higher than the label-recommended dose for narcolepsy. MPH monotherapy was typically provided in divided dosages (3-4 times daily) of regular-release or as a combination of sustained-release and regular-release formulations (Ali 2009). The MPH doses used to treat narcolepsy and IH from observational studies are listed in Table 2. Daily doses up to 60-80 mg Ritalin, and occasionally up to 100-300 mg Ritalin, have been used in adults (Mitler and O'Malley 2005).

In addition, several publications report on the use of daily MPH doses higher than 80 mg. For example, single oral doses of 90 mg Ritalin (bolus dose) have been administered in 49 recreational drug users (Parasrampuria 2007), with a reported mean peak (C_{max}) MPH plasma concentration of 38.8 ng/mL and AUC_{inf} of 195 h.ng/mL. Prescribed multiple oral doses ranging 30-600 mg of IR

and/or ER MPH formulations (median dose: 160 mg) have been recently reported in 28 patients with ADHD and SUD (Arvidsson 2022), with d-MPH plasma concentrations ranging between 8 and 472 ng/mL (median 31.6 ng/mL).

Based on these data, the d-MPH exposure after 80 mg/day Ritalin is a reliable estimate of the upper exposure of Ritalin to treat daytime sleepiness in most patients with sleep-related disorders and was therefore chosen as a starting point for predicting the highest exposure of SDX-derived d-MPH needed to treat IH patients. The molar-equivalent dose of long-acting MPH (80 mg/day Ritalin LA) was used as a second point of reference. The predicted mean d-MPH plasma concentration-time profiles after daily doses of 80 mg Ritalin either administered daily as 2 individual doses of 40 mg Ritalin (IR) 5 hours apart, or as 80 mg Ritalin LA, are shown in Figure 3 (simulations are based on the PK profiles in the Ritalin LA® US Prescribing Information 2021). The predicted mean d-MPH plasma concentration-time profiles after the SDX doses used in the current study (single daily doses of 80, 160, 240, and 320 mg SDX) are also shown in Figure 3 (simulations are based on the PK profiles observed in Study KP879.101). The highest dose of 320 mg/day SDX was chosen such that its associated predicted mean d-MPH peak concentration is not larger than the predicted peak concentration after 80 mg/day Ritalin (IR) and Ritalin LA.

The current study may inform about optimal SDX dose range and the best dose regimen (nighttime dosing or bid) for further studies in patients with IH. The nighttime dosing regimen is of interest since there is little or no exposure to d-MPH for the first several hours post-dose and the mean peak d-MPH concentration occurs at 10-12 hours post-dose (Figure 2 and Table 1).

The extensive clinical data collected with SDX (see KP1077 Investigator's Brochure) has provided understanding of the performance of the molecule under a broad range of conditions that include different subjects (children, adolescents, and adults), doses (ranging from 6 mg to 600 mg SDX Cl), durations of dosing (up to one year of once-daily administration), routes of administration (oral, intranasal, and intravenous) and feeding conditions (fasted vs. fed). The collective findings of all clinical studies conducted with SDX indicate that the conversion of SDX to d-MPH is a consistent, predictable, and well-controlled process, and that SDX is not associated with new or unusual safety concerns at SDX doses in the SDX dose range used in the study. In addition, for the safety of the subjects, and typical for dosing with CNS stimulants, daily doses of SDX will be titrated from the lowest dose (80 mg/day) to the optimized dose based on individual tolerability and effect, up to a maximum of 320 mg/day.

Table 2. Published Methylphenidate Treatments of Daytime Sleepiness in Patients with Narcolepsy and Idiopathic Hypersomnia

Reference	Type of Study	Disease	No of Subjects	Range of Daily Dose of MPH	Efficacy	Most Common Side Effects
Daly and Yoss 1956	Case series	Narcolepsy	25	***40-240 mg Ritalin***	Good to excellent in 84%	NR
Yoss and Daly 1959	Case series	Narcolepsy	60	***40-80 mg Ritalin*** [a]	Good to excellent in 68%	Nervousness and tremulousness (35%); anorexia (22%), insomnia (17%), palpitations (3%)
Akimoto 1960	Case series	Narcolepsy	80	***20-80 mg Ritalin***	Disappearance of sleep attacks	NR
Honda 1979	Observational	Narcolepsy	106	***10-60 mg***	Improved in 92% (GIR)	Dry mouth (38.6%), sweating (34.9%), headache (24.5%), stomach discomfort (21.6%), and loss of appetite (16.9%)
Mitler 1994	Observational	Narcolepsy	13	***10-60 mg***	Improved EDS by MWT	NR
Reinish 1995	Observational	Narcolepsy	11	***10-70 mg***	Lengthened sleep and REM latency by MWT	Loss of appetite, headaches
Ali 2009	Retrospective database review	IH	61	***15-85 mg*** [b]	Complete response in 41% and partial response in 21% (disease severity)	Nervousness (~25%), palpitations (~15%), and insomnia (~10%)

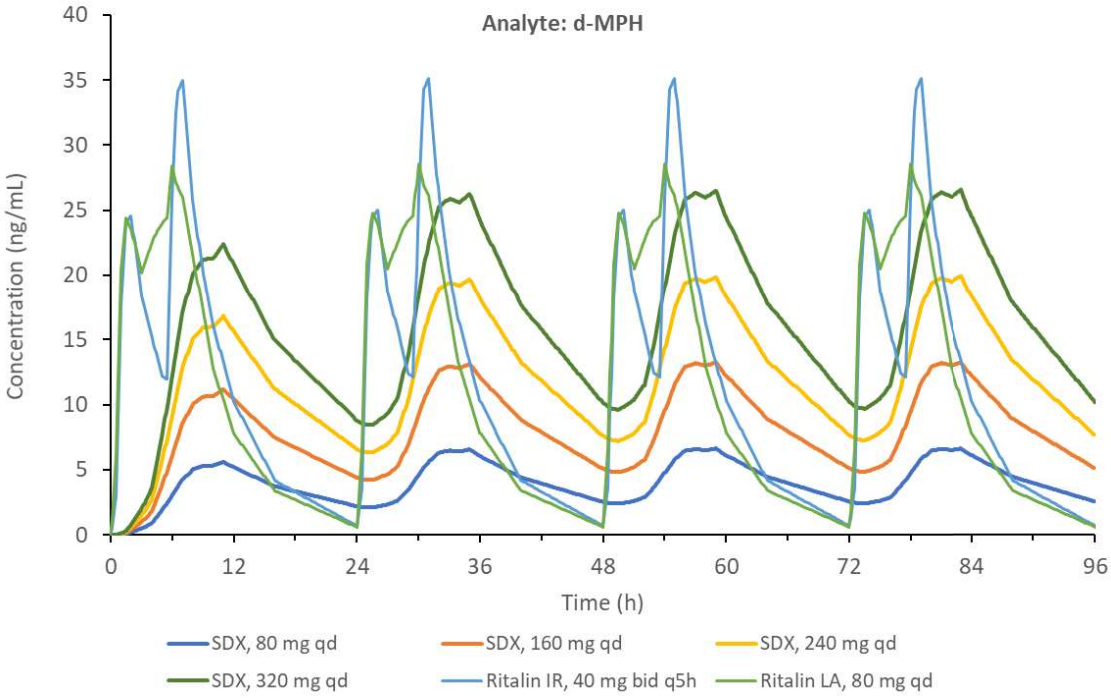
IH = Idiopathic Hypersomnia; EDS = Excessive Daytime Sleepiness; GIR = Global Improvement Rating; MWT = Maintenance of Wakefulness Test; NR= Not Reported

Table is based on Mitler and O'Malley 2005, supplemented with additional studies.

a. Median Ritalin dose was 60 mg/day; one subject took 300 mg MPH.

b. Mean daily dose ± SD reported was 50.0 ± 27.3 mg; dose range listed in this table was approximated by calculation of the 10^{th} and 90^{th} percentile.

Figure 3. Simulated d-MPH Plasma Concentration-Time Profiles to Steady State After Daily Oral Administration of SDX, Ritalin (IR), and Ritalin LA



Simulations are based on the plasma concentration-time profiles after single oral doses of 240 mg SDX Cl (Study KP879.101), 20 mg Ritalin (Ritalin® US Prescribing Information 2021), and 40 mg Ritalin LA (Ritalin LA® US Prescribing Information 2021). Simulations were performed by dose-proportional scaling to higher doses and to steady state by nonparametric superposition in Phoenix WinNonlin, Certara.

4.2. Justification of Efficacy Assessments

4.2.1. Safety Assessments

The use of vital signs, body weight, ECGs, clinical laboratory tests, standard AE reporting, physical examinations, and questionnaires selected to assess the safety of the drug (suicidal ideation assessment using the C-SSRS) are appropriate since they are routinely used to assess the safety profile of drug in clinical studies, and some are pertinent to known risks of d-MPH products, including SDX. The C-SSRS is a validated questionnaire used to determine the clinically meaningful risk of a subject's immediate risk of suicide (Posner 2011), in clinical studies and acute care settings.

The sleep quality (evaluated as a safety assessment) will be rated using question #6 of the Pittsburgh Sleep Quality Index (PSQI) (Buysse 1989). The PSQI is a validated patient-reported global measure of nocturnal sleep disturbance that has been used in clinical trials in a variety of diseases. Question #6 of the PSQI (PSQI-Q6) has also been used to evaluate nocturnal sleep quality in patients with narcolepsy treated with sodium oxybate, modafinil ,

and their combination (Dauvilliers 2017).

4.2.2. Efficacy Assessments

The primary efficacy endpoint in the current study is the change from baseline of the Epworth Sleepiness Scale (ESS) score to assess EDS. The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness in narcolepsy (Johns 1991, Johns 2000, Broderick 2013). The ESS has also demonstrated sensitivity to pharmacotherapies used to treat EDS in IH and other central disorders of hypersomnolence (Mayer 2015, Trotti 2015, Trotti 2016, Inoue 2021, Dauvilliers 2022). A clinically significant reduction in ESS score of 2 points in patients with central disorders of hypersomnolence was suggested in the current treatment guidelines from the American Academy of Sleep Medicine (Maski 2021).

While EDS is reported by virtually all patients with IH, many also report sleep drunkenness (ie, severe sleep inertia) and long (>1 hour) daytime naps that are typically unrefreshing (Vernet 2010, Trotti 2020). Patients with IH also frequently complain of impaired executive functioning (e.g., cognitive and attentional difficulties, "brain fog", poor memory), fatigue, decreased alertness, depressive symptoms, and automatic behaviors, all of which contribute to overall disease burden and poor quality of life (Vernet 2010, Trotti 2020, Schneider 2021a, Schneider 2021b). For example, in a recent survey of 468 IH patients enrolled in the Hypersomnia Foundation registry, "brain fog" (defined as "being unable to think clearly or concentrate at any time throughout the day") and poor memory were experienced by 82.6% and 71.8% of patients, respectively (Trotti 2020).

After excessive daytime sleepiness (experienced by nearly all IH patients),"brain fog" — defined as "being unable to think clearly or concentrate at any time throughout the day" (Trotti 2020) — is the second most common symptom (experienced by approximately 83% of patients) in patients with IH. The Brain Fog scale that will be used in the current study was adapted from Ross 2013, who applied the scale to evaluate symptoms, frequency and severity of Brain Fog, effects on functioning, and the possible triggers through a self-reported survey in 132 patients with Postural Orthostatic Tachycardia Syndrome (POTS). The top two reported brain fog triggers were fatigue and a lack of sleep. Of note, 32% of patients reported having a diagnosed sleep disorder, most commonly insomnia, sleep apnea, or restless leg syndrome, and 67% of all patients reported taking stimulant medications to treat their brain fog.

The IHSS is a validated and reliable instrument to evaluate the severity and functional consequences of symptoms of IH, and is sensitive to clinical changes following treatment (Dauvilliers 2022, Rassu 2022).

Additionally, the CGI-S and PGI-S have been used extensively in clinical studies to assess global clinician-reported and patient-reported outcomes.

The Karolinska Sleepiness Scale (KSS) is frequently used for evaluating at-the-moment subjective (patient-reported) sleepiness. The validity and reliability of the KSS was demonstrated (Kaida 2006) by good agreements with electroencephalographic, behavioral and other subjective indicators of sleepiness (including the Psychomotor Vigilance Task, PVT). Therefore, KSS ratings are a useful, reliable and valid proxy for EEG or behavioral indicators of sleepiness. KSS assessments are administered easily, sensitive to manipulations known to affect sleepiness, correlate with impaired waking function and appear to be used consistently across individuals (Akerstedt 2014).

The Patient Reported Outcomes Measurement Information System (PROMIS, Cella 2010) is a generalizable and universal measure of patient-reported outcomes to assess many health-related quality-of-life domains. PROMIS, developed by the National Institutes of Health (NIH), is the most extensively validated measurement system of health status (physical, mental, and social domains) in the world (van Balen 2021). It has undergone extensive psychometric testing for validity and reliability in a number of diseases (Tang 2019). In the current study, the health domains of Fatigue, Ability to Participate in Social Roles and Activities, and Depression of PROMIS®-29 (Hays 2018) will be used.

The ZOGIM-A questionnaire (Shapiro 2006) was created as an efficient measure of wakefulness, as an instantaneous alternative to the Maintenance of Wakefulness Test (MWT). The scale evaluates a subject's experiences with alertness over the course of the day, with focus on the psychological and daily functioning aspects. The scale has been validated with respect to reliability and validity, and scores were statistically significantly different between patients with and without narcolepsy (Shapiro 2006).

Sleep Inertia, defined as a transitional state between sleep and wake marked by decreased arousal and impaired performance (Hayashi 2005) will be assessed by a Sleep Inertia Visual Analog Scale (SIVAS). This scale has demonstrated sensitivity to changes in sleep inertia caused by afternoon napping (Takahashi and Arito 2000) and after treatment of IH patients with oxybate (Dauvilliers 2022).

Patient-reported daily sleep diaries will be used to conveniently report sleep/wake patterns on a day-to-day basis throughout the study to assess eligibility and efficacy. This method of assessing the Total Sleep Time (TST) is used in clinical practice and research in IH (Dauvilliers and Buguet 2005, Dauvilliers 2017), as it provides a measure of sleep in the home environment over a longer period of time than is feasible in a sleep laboratory.

4.2.3. Pharmacokinetic Assessments

Blood samples will be collected for the measurements of SDX, SDX-derived d-MPH, and ritalinic acid (a major inactive metabolite of d-MPH), which will be subsequently used to calculate the PK parameters in IH subjects with standard PK methods. The timepoints were selected to optimally capture these standard PK parameters.

5. STUDY OBJECTIVES

5.1. Primary Objective

To determine the safety and tolerability of SDX in treating adults with IH.

5.2. Secondary Objectives

- To explore the efficacy of SDX in adults with IH. The study may inform about the best dosing regimen, optimal dose range, duration of treatment, and secondary endpoints for a future Phase 3 study.

- To characterize the steady-state pharmacokinetics (PK) following administration of SDX in subjects with IH.

6. INVESTIGATIONAL PLAN

6.1. Study Design

The study is a Phase 2, placebo-controlled, double-blind, randomized withdrawal study to determine the safety, efficacy and pharmacokinetics of oral SDX in patients with IH.

The study will consist of the following visits:

- **Screening Period:** Subjects will undergo a screening period up to 35 days prior to entering the Open-Label Titration period.

- **Open-Label Titration Period:** Subjects will attend weekly clinic visits for a period of 5 weeks. The subject's treatment will be titrated (change of dose as needed) to an optimal daily dose of SDX starting with the lowest dose (see Section 8), based on individual tolerability and effect.

- **Double-Blind Randomized Withdrawal Period:** This period will consist of 2 weeks during which the subjects will receive the optimized dose. The subjects will have clinic visits at the beginning and end of the period. At the start of the Withdrawal Period, subjects within each treatment group of the Titration Period

will be randomized in a 2:1 ratio to SDX or placebo.

- **Follow-Up Phone Call:** 1 week after administration of the last dose of the double-blind randomized withdrawal period, site staff will conduct a follow-up phone call with the subject to evaluate safety parameters.

6.2. Study Duration

Subjects will participate in the study as outpatients for up to 94 days, a screening period up to 35 days , a 35-day Open-Label Titration Period, a 14-day Double-Blind Withdrawal Period and a Follow-Up Phone Call 7 ±3 days after the administration of the last dose of the Double-Blind Withdrawal Period.

6.3. Dose Escalation Stopping Rules

The highest dose of study drug used at any given time in the study will be limited to a study-specific maximum tolerated dose (MTD), expressed in mg/day (daily dose). The MTD will be evaluated and changed, if needed, based on safety data collected as the study proceeds. Subjects will be enrolled in the study on a rolling basis over several months and at different study sites. The data needed to evaluate overall safety and tolerability at any dose level will become available on a rolling basis as the study progresses.

The following "Critical Safety Criteria" will be used to decrease a subject's individual dose, to decrease the MTD (ie, a decrease of the maximum dose used in all subjects of a particular dosing regimen cohort), and to evaluate early termination of dosing regimen cohort, or both dosing regimens (ie, early termination of the study):

- Clinically significant vital signs, ie, heart rate and/or blood pressure exceeding Critical Vital Sign thresholds (see Section 13.5.2 for definition and repeats)
- Clinically significant ECG abnormalities.
- Intolerable insomnia (ie, continuous, lasting >24 hours, or intolerable by the subject).
- Hypervigilance, restlessness, or euphoria, intolerable by the subject or judged intolerable by the Investigator or designee.
- Drug-related serious AEs (SAEs).

The following overall escalation stopping rules will be used:

- The dose escalation rules will be applied separately within each dosing regimen group (qd pm and bid).
- The MTD for each dosing regimen is defined as the next lower dose level than the dose level after which any of the following occurs:
  - Twelve (12) subjects (50% of the intended number of 24 subjects enrolled in total) experience an event included in the Critical Safety Criteria listed above.
  - The Investigator and the Sponsor consider that the number and/or severity of all AEs justify discontinuation of dose escalation to a particular dose level.
- If the MTD for a particular dosing regimen drops below the highest dose level used in the study for that dosing regimen, the following actions will be taken:
  - In remaining to-be-enrolled subjects: dose escalation during the Titration Period will be limited to the MTD for the particular dosing regimen.
  - In subjects who are receiving study drug in the study (Titration Period or Withdrawal Period): the daily dose level for the particular dosing regimen will be decreased to the MTD.

6.4. Study Early Stopping Rules/Early Study Termination

In the unlikely event that the study-specific MTD (Section 6.3) falls below the lowest daily dose (80 mg SDX) within a particular dose regimen group, the study will be stopped for this particular dose regimen group. If both dosing regimen groups are terminated early, the study will be stopped early.

The following termination procedures will be performed at early stopping of a dosing regimen group: All subjects in the terminated dosing regimen group will be withdrawn; subjects will be contacted by study site staff and will be instructed to stop taking study drug. An Early Termination Visit will be scheduled, and Early Termination procedures will be completed.

7. SUBJECT SELECTION

7.1. Number of Subjects

An appropriate number of subjects will enter the Screening Period and complete the Titration Period, to randomize at least 48 subjects (24 subjects for each dosing regimen) in the Withdrawal Period. Screening and enrollment of new subjects will continue until at least 48 subjects are randomized in the Withdrawal Period. The required number of subjects may be increased based on the interim analysis (Section 18.3.5).

7.2. Study Population

Adults 18 years of age and older with IH who meet the inclusion/exclusion criteria listed below.

7.2.1. Inclusion Criteria

A subject will be eligible for inclusion in the study if all the following criteria apply:

1. Male or female at least 18 years of age at the time of consent.
2. Subject's Body Mass Index (BMI) must be ≤35 kg/m^2.
3. Has a primary diagnosis of IH (lifetime) according to the International Classification of Sleep Disorders (ICSD-3) criteria (Appendix B). If documentation of IH diagnosis is unavailable in the screening window, diagnostic testing must be performed according to the ICSD-3 criteria. This may include one of the following to confirm the diagnosis of IH:
    a. Nocturnal polysomnogram (PSG) followed by a multiple sleep latency test (MSLT). The duration of the MSLT must be long enough to include at least 4 naps.
    b. 24-hour PSG
    c. Wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).
4. At the Screening Visit and Visit 2, subjects must have Epworth Sleepiness Scale (ESS) scores ≥11 (as assessed with a look-back period of 1 week).
5. Average nightly Total Sleep Time (TST) of ≥7 hours, per subject history. The average TST will be confirmed by Investigator's review of sleep diaries collected during the 10 days prior to Visit 2 (last 10 days of the Screening Period).
6. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis) at Screening. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant.
7. Subjects must give written consent.

8. If currently treated with nicotine replacement therapy, must have been taking the same regimen and dose for at least 2 months prior to screening and must agree to take the same dose during the Titration Period and Withdrawal Period.

9. Subjects must be able and willing to wash out prohibited medications to treat IH and all medications that can affect wakefulness and sleep, including herbal medications. If a subject has received any of the therapies listed in this protocol, a washout-period of at least 14 days, or equivalent to 5 half-lives of the drug, whichever is longer (and at least 30 days for sedating antidepressants; 14 days for CNS stimulants), is required prior to the first dose of study drug. Subjects must abstain from these medications during the study until the Follow-Up Phone Call or Early Termination. Patients may be switched from a sedating to a non-sedating antidepressant as long as the switch occurs at least 14 days before Visit 2.

10. Have used a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception.. Female subjects must agree to use one of the following forms of birth control from Screening until at least 30 days after the last dose of study drug, unless a different timeframe is listed below:

    a) Vasectomized partner (at least 6 months prior to Screening).

    b) Post-menopausal (no menses for at least 12 months prior to Screening).

    c) Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to Screening.

    d) Non-surgical sterilization (eg, Essure® procedure) at least 3 months prior to Screening.

    e) Double barrier (diaphragm with spermicide; condoms with spermicide)

    f) Intrauterine device (IUD)

    g) Total abstinence (must agree to use a double barrier method if they become sexually active between Screening and 30 days after the last dose of study drug).

    h) Implanted or intrauterine hormonal contraceptives in use for at least 3 consecutive months prior to Screening.

    i) Oral, patch, or injected contraceptives, or vaginal hormonal device (ie,

NuvaRing®), in use for at least 3 consecutive months prior to Screening.

11. Male subjects must have had a vasectomy (at least 6 months prior to Screening) or must agree to use one of the following forms of birth control from Screening until 90 days after the last dose of study drug:

    a. Double barrier method (diaphragm, condoms, contraceptive sponge, or vaginal ring, all with spermicidal jelly or cream).

    b. Total abstinence (must agree to use a double barrier method if they become sexually active during the period from screening to 90 days after the last dose of study drug).

12. Subject must understand and be willing and able to comply with all study procedures and visit schedule, including completion of all forms and questionnaires that the subject will need to fill in daily while at home.

7.2.2. Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be enrolled into the study:

1. Hypersomnia due to another medical, behavioral, or psychiatric disorder condition (eg, narcolepsy, depression disorders, multiple sclerosis, Parkinson's disease, stroke). This includes history of cataplexy, history or screening MSLT showing ≥2 Sleep Onset REM Periods (SOREMPs), or history or screening PSG SOREMP <15 minutes.

2. Evidence of clinically significant sleep-related breathing disorders, including any of the following:

    a. Presence of clinically significant (moderate or worse) obstructive or central sleep apnea as determined by the Investigator or documented within the last 10 years.

    b. Current diagnosis of clinically significant sleep apnea including being treated with Continuous Positive Airway Pressure (CPAP) therapy or any other treatment of sleep apnea.

    c. Obstructive Apnea Hypopnea Index (AHI) >15 episodes per hour on any test within the last 10 years or during the Screening PSG (if conducted).

    d. Clinically significant hypoventilation.

3. Clinically significant parasomnias (eg, sleep walking, rapid eye movement [REM] sleep behavior disorder, etc).

4. Periodic Limb Movement Disorder (PLMD) Arousal Index (PLMA-I) >15 during the Screening PSG (if performed) or from a test during the last 10 years (ie, historical diagnosis of PLMD), or a PLMD diagnosis older than 10 years with current (last 60 days) treatment and/or symptoms of rhythmic movements involving one or both legs during sleep.

5. Occupation requiring nighttime shift work or variable shift work with early work start times (ie, before 6 AM), if this occurs more than once per week.

6. Any planned travel during the study that includes more than 3 time zones, or planned travel that includes 3 time zones on more than 2 occasions during the study.

7. Going to sleep for the night later than 1 AM at a frequency of more than once per week.

8. Current or past (within 1 year) major depressive episode according to DSM-5 criteria. Patients with depression under control are allowed per the judgment of the Investigator, but the antidepressant treatment must be non-sedating, stable for at least 6 months prior to Screening and expected to remain stable for the duration of the study.

9. Has any history of attempted suicide (lifetime) or clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment at Screening.

10. Any clinically significant unstable medical abnormality, chronic disease (eg, asthma or diabetes), or a history of a clinically significant abnormality of the cardiovascular (including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension), central nervous system (eg, neurodegenerative disease, seizure disorder or history of head trauma associated with loss of consciousness), gastrointestinal, respiratory (eg, compromised respiratory function), hepatic, or renal systems, or a disorder or history of a condition (eg, malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion of study drug. Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Monitor should be consulted. Any subject with a known cardiovascular disease

or condition (even if controlled) must be discussed with and approved by the Medical Monitor during Screening.

11. Subject should be excluded from the study with any of the following vital signs at Screening:

    a. a confirmed systolic blood pressure outside the range of 90-145 mmHg.

    b. a confirmed diastolic blood pressure outside the range of 50-90 mmHg.

    c. a confirmed resting heart rate outside the range of 40-100 beats per minute.

12. History or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant, including the following:

    a. ECG findings of ischemia or infarct

    b. Complete bundle branch blocks

    c. Symptomatic arrhythmias as ventricular arrhythmias (non-sustained ventricular tachycardia (VT), multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal or any predominantly non-sinus-conducted rhythm.

    d. QTcF >450 msec for males or >470 msec for females, on Screening ECG.

    e. PR interval outside the range of 120 to 220 msec on Screening ECG.

13. Estimated glomerular filtration rate (GFR) at screening <60 mL/min/1.73 m^2 using the CKD-EPI 2009 method (Chronic Kidney Disease Epidemiology Collaboration, Levey 2009).

14. Malignant neoplastic disease requiring therapy within 2 years prior to Screening or during the study, or clinically relevant as judged by the Investigator.

15. Uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening.

16. Laboratory value for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limits of normal (ULN).

17. Excessive caffeine use during the 10 days prior to Visit 2 or anticipated excessive use defined as >600 mg/day of caffeine during the Titration Period and Withdrawal Period.

18. Treatment or planned treatment with prohibited medications (see list) or unwilling to refrain from any prohibited medications. Treatment must have been discontinued 14 days or 5 half-lives, whichever is longer, prior to the first dose of study medication (and at least 30 days for sedating antidepressants; at least 14 days for CNS stimulants). The Investigator must ensure that discontinuation from these medications is medically supervised.

19. Current or past substance use disorder (including alcohol and psychoactive cannabinoids) according to DSM-5 criteria; current or past history of substance abuse treatment (including alcohol), or the subject is unwilling to refrain from substance use (including alcohol) during the study. Past is defined as within 12 months prior to Screening.

20. Nicotine dependence that has an effect on sleep (eg, a subject who routinely awakens at night to smoke).

21. Evidence of substance or alcohol use or has a positive urine or breath alcohol or positive urine drug screen at Screening. Urine or breath will be tested for alcohol, and urine will be tested for drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone) and methylphenidate (MPH) at Screening (Visit 1) and at Visit 2. A urine dipstick will be used to screen for the presence of MPH in the urine. Subjects with a positive urine drug screen (eg, amphetamines, methylphenidate) may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required (test at Visit 2 needs to be negative). Subjects with a positive test at Screening may be retested (test at Visit 2 needs to be negative).

22. Female subjects who are pregnant, breastfeeding, or lactating, or plan to become pregnant during the duration of the study.

23. Participation in any other clinical study with an investigational drug/product within 30 days prior to Screening or is currently participating in another clinical trial.

24. Subject has poor ePRO compliance during the last 10 days of the Screening Period (evaluated at Visit 2), at the discretion of the Investigator.

25. Subject has commitments during the study that would interfere with attending study visits.

26. Subject anticipates a move outside the geographic range of the investigative site during the study period or plans extended travel inconsistent with the planned study visits.

27. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

7.3. Rescreening Rules

Subjects may be allowed to rescreen if they previously did not meet all eligibility requirements at the Screening Visit. Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, uncontrolled thyroid disorder, electrolyte abnormalities) and with the approval of the Investigator. Only those screening procedures that did not meet the eligibility criteria need to be repeated , may only be repeated once, and need to be repeated within the screening window.

Subjects who failed screening due to a Total Sleep Time of <7 hours based on the sleep diaries collected during the 10 days prior to Visit 2, will not be rescreened. If a PSG/MSLT was performed during the Screening Period, it will be done only once (no rescreen unless performed with errors).

Subjects who have exceeded the time window allowed for screening to complete all screening assessments or have failed some of the inclusion/exclusion criteria with no time left to rescreen within the screening window, may be rescreened (full rescreen) for participation later during the enrollment phase of the study, at the discretion of the Investigator. This full rescreen may be conducted once.

Subjects who received any dose of study drug and are terminated early, are not eligible to participate later in the study (and will not be rescreened).

8. STUDY TREATMENTS

8.1. Open-Label Titration Period

Subjects will attend weekly clinic visits for a period of approximately 5 weeks. The subjects will have clinic visits at weekly intervals (Visits 2, 3, 4, 5, 6, and 7) with allowed windows of ±3 Days between visits. Visit 7 is both the end of the Titration Period and the start of the Withdrawal Period. The subject's treatment will be titrated (change of dose as needed) to an optimal daily dose of SDX starting with the lowest dose, based on individual tolerability and effect. Study drug may be taken with or without food. The 4 possible SDX doses to be taken orally are:

- 80 mg/day SDX
- 160 mg/day SDX
- 240 mg/day SDX
- 320 mg/day SDX

The subjects will be randomized to one of the following dosing regimens:

- **Treatment X**: SDX, once daily at night (qd pm)
- **Treatment Y**: SDX, half the daily dose in the morning and at night (bid)

Randomization will be stratified by gender. The randomized assignment to one of the dosing regimens and the SDX dose size will not be blinded.

8.2. Guidance for Dose Titration

During the 5-week Open-Label Titration Period, the dose of SDX will be titrated on an individual basis to an optimal daily dose, as follows:

- The starting dose of SDX (starting at the Visit 2 day) will the lowest dose in the study (80 mg SDX).
- At the subsequent visits of the Titration Period, at approximately weekly intervals, a subject's dose will be increased, decreased, or kept the same based on individual tolerability and effect, at the discretion of the Investigator.
- If subjects experience dose-limiting adverse events (AEs) while at home, they need to contact their study site, and the Investigator has the option to decrease the dose before the next visit. An unscheduled visit may occur to evaluate a subject's health status and to replace the study medication with a lower dose of SDX.

  Note: "at home" in this study protocol means "not at the study site".
- At any time, the daily dose of SDX will be only one of the following: 80, 160, 240, or 320 mg/day, with the following exceptions:
  - Subjects with a lack of tolerability at a certain dose level may be instructed by the study site to stop taking study drug until they can be evaluated during an unscheduled visit at which time, they might receive new drug supplies at a lower SDX dose.
  - Subjects who are assigned to the bid dosing regimen, when their dose change occurs in the middle of a single day, may receive am and pm doses that are each based on a different total daily dose.

Although the assessments of individual tolerability and effect, and a potential subsequent

dose change, are at the discretion of the Investigator, the following guidelines should be taken in consideration:

- In general, if the current daily dose of SDX is tolerated and there appears to be an opportunity to further decrease the subject's IH severity, the SDX dose can be escalated to a higher dose level (to a maximum of 320 mg SDX).
- The main efficacy assessment for guiding the dose titration is the ESS. The objective of the dose titration is to decrease a normal ESS score (<11) during the Titration Period (in concert with the assessment of tolerability). A normal range of daytime sleepiness in healthy adults corresponds to an ESS score ≤10 (Johns 1991), with scores of 11-14 for mild, 15-17 for moderate, and 18-24 for severe daytime sleepiness.
- A secondary efficacy assessment for guiding the dose titration is the PGI-S. The objective is to decrease the PGI-S by at least 1 point during the Titration Period.
- Inadequate tolerability includes the occurrence of a drug-related SAE or an AE during the administration of a dose level that, in the opinion of the Investigator, would not be in the best interest of the subject to be continued, or that, in the opinion of the subject, causes undue discomfort.
- Other safety criteria to limit dose escalation (or to decrease the dose) are listed in Section 6.3.

8.2.1. Dose Titration Window

The time interval from Visit 2 to Visit 6 is the intended period for dose titration. It is the intention that the dose during the last week of the Titration Period (Visit 6 to Visit 7) is the same as during the previous week, although, mainly for safety and tolerability, it is at the Investigator's discretion to change the dose at Visit 6 (at any time before Visit 7). The optimized dose for the Withdrawal Period will be determined at Visit 7, although some patients will have received this daily dose for a while in the Titration Period.

In addition, if possible, subjects will need to have received the same daily dose of study drug for at least 3 consecutive days immediately before the PK Visit. This dose is not necessarily the optimized dose (the optimized dose for the Withdrawal Period will be determined at Visit 7). The PK Visit may coincide with Visit 6 or may occur at a separate day after Visit 5 and before Visit 7 (Section 9.2.5).

8.3. Eligibility Criteria for Enrollment in the Withdrawal Period

Subjects are eligible to continue in the Withdrawal Period of the study if the following criteria are met at the end of the Titration Period (Visit 7):

1. Subjects demonstrate adequate compliance with dosing in the Titration Period. Adequate compliance in the Titration Period is defined as 80-100% based on study drug accountability since Visit 2. Subjects may also be withdrawn early (even if their numerical compliance in the Titration period is within 80-100%) at the discretion of the Investigator, if the Investigator expects poor compliance in the Withdrawal Period (for example, when subjects lost or failed to return unused study drug on multiple occasions during the Titration period).
2. No ongoing AEs occur due to SDX treatment that would require dose adjustment or early discontinuation during the Withdrawal Period.
3. Subjects must have a decrease of their ESS score of at least 2 points at Visit 7 compared to the titration baseline (Visit 2).

Subjects who are not eligible to continue in the Withdrawal Period will be withdrawn, and Early Termination procedures will be completed during an Early Termination visit (see Section 9.6). The reason for lack of eligibility will be recorded.

8.4. Double-Blind Withdrawal Period

This period will consist of approximately 2 weeks (14 days with an allowed window of ±3 days) during which the subjects will receive their individual optimized dose. The subjects will have clinic visits at the beginning and end of the period (Visit 7 and Visit 8). At the start of the Withdrawal Period, subjects within each treatment group of the Titration Period will be randomized in a 2:1 ratio to SDX or placebo.

- Subjects receiving Treatment X (qd pm regimen) in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period:
    - **Treatment A:** SDX, once daily at night (qd pm)
    - **Treatment B:** Placebo, once daily at night (qd pm).
- Subjects receiving Treatment Y (bid regiment) in the Titration Period will be randomized to receive one of the following treatments in the Withdrawal Period:
    - **Treatment C:** SDX, half the daily dose in the morning and at night (bid)
    - **Treatment D:** Placebo, half the daily dose in the morning and at night (bid).

The randomization will be stratified by optimized dose. Subjects will keep taking study drug qd pm or bid (pm and am) as assigned by the randomization at the start of the Titration Period. The randomized assignment to either SDX or placebo (Treatments A vs B, and C vs D) will be blinded; the SDX dose size (optimized dose) will not be blinded. Study drug may

be taken with or without food.

8.5. Dosing Regimens

The possible doses of study drug administered daily in the Titration and Withdrawal Periods are listed by daily dose and dosing regimen in the following table:

Daily Dose (mg)		Equimolar d-MPH HCl Dose (mg)	Treatments [a]					
			X and A	B	Y and C		D	
			qd	qd	bid		bid	
SDX	SDX Cl		pm	pm	am	pm	am	pm
80	85.7	43.1	2 x 40 mg SDX	2 x placebo	1 x 40 mg SDX	1 x40 mg SDX	1 x placebo	1 x placebo
160	171.3	86.2	2 x 80 mg SDX	2 x placebo	1 x 80 mg SDX	1 x 80 mg SDX	1 x placebo	1 x placebo
240	257.0	129.4	2 x 120 mg SDX	2 x placebo	1 x120 mg SDX	1 x 120 mg SDX	1 x placebo	1 x placebo
320	342.7	172.5	2 x 160 mg SDX	2 x placebo	1 x 160 mg SDX	1 x 160 mg SDX	1 x placebo	1 x placebo

SDX = Serdexmethylphenidate; qd = once-per-day; bid = twice daily

a. Treatments are expressed as number of capsules, capsule strength, and active ingredient (SDX) or placebo

Treatments X and Y are open-label, administered during the Titration Period;
Treatments A vs B, and C vs D are blinded, administered during the Withdrawal Period.
am administration: in the morning, shortly after awakening.;
pm administration: in the evening, just before going to sleep.
Study drug may be taken with or without food.

8.6. Blinding

Open-Label Titration Period: The randomized assignment in the beginning of the Titration Period to each of the dosing regimens (qd pm or bid) will not be blinded. The dose level that may change for each subject as the Titration Period progresses (1 of 4 possible dose levels) will not be blinded.

Double-Blind Withdrawal Period: The randomized treatment assignment within each dosing regimen (qd pm and bid), in the beginning of the Withdrawal Period, of either SDX or placebo will be blinded (Treatments A vs B, and C vs D). Neither the subject, the Investigator, or the Sponsor will know the subject's treatment assignment of active drug versus placebo. The dosing regimen and optimized dose level (1 of 4 possible dose levels) will not be blinded.

Upon completion of the study and after the database is locked, the Withdrawal Period randomization codes will be provided by the unblinded statistician to unblind the study.

Emergency unblinding of patients (Withdrawal Period): Under normal circumstances, the blind will not be broken until subjects have completed treatment. The blind for individual subjects can be broken before study unblinding at the request of the Investigator only if a specific emergency treatment would be dictated by knowing the treatment status of a subject. When knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject, the Investigator should contact the CRO's Medical Monitor (or designee). Prior to unblinding the subject's treatment assignment, the Investigator should assess the relationship of an AE to the administration of the study drug (Yes or No). The Investigator must then contact the CRO's Medical Monitor to unblind an individual patient's treatment assignment. If the blind is broken for any reason, the Investigator must record the date and reason for breaking the blind on the appropriate electronic Case Report Form (eCRF) and source documents. If an SAE is reported, the CRO's Medical Monitor (or designee) may unblind the treatment assignment for an individual subject for expedited regulatory reporting requirements.

8.7. Compliance

Quantities of all study drug dispensed and returned will be recorded by each site's staff member or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site. In addition, quantities of unaccounted drug (drug lost and/or not returned by the subjects) will be recorded with reasons or possible reasons, as available. Study sites will attempt to fully account for all drug supplies.

Acceptable compliance is defined as 80-100% (inclusive). If compliance between subsequent scheduled visits is outside this acceptance range, or cannot be determined (when, for example, the subject did not return unused study drug), the Investigator or designee will counsel the subject. If a subject is noncompliant more than once, the Investigator will discuss the subject's noncompliance with the Medical Monitor. Subjects with a repeated lack of acceptable compliance (at the discretion of the Investigator) may be withdrawn early from the study (at the discretion of the Investigator).

Subjects must demonstrate adequate compliance with dosing in the Titration Period. Adequate compliance in the Titration Period is defined as 80-100% based on study drug accountability since Visit 2. Subjects may also be withdrawn early (even if their numerical compliance in the Titration period is within 80-100%) at the discretion of the Investigator, if the Investigator expects poor compliance in the Withdrawal Period (for example, when subjects lost or failed to return unused study drug on multiple occasions during the Titration period).

Compliance will be reported by treatment in the CSR, separately for the Titration Period and Withdrawal Period, and overall.

9. STUDY PROCEDURES

The study will consist of a Screening Visit, an Open-Label Titration Period, a Double-Blind Withdrawal Period, and a Follow-Up Phone Call. A table for the Schedule of Events (SOE) representing the required testing procedures to be performed is included in Section 1. Following is a list of these procedures and assessments.

9.1. Screening Procedures

Subjects will complete the screening visit (Visit 1) within 35 days (the screening window) of starting the Open-Label Titration Period (Visit 2). See Section 7.3 for rescreening rules for potential rescreening of subjects who did not meet all eligibility requirements at the Screening Visit, or for subjects who have exceeded the time window allowed for screening.

Prior to conducting any study-related activities including screening procedures, written consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

The following procedures will be performed at the Screening Visit:

1. Permission and HIPAA authorization by the subject.
2. Written consent by the subject.
3. IH diagnosis and confirmation according to the International Classification of Sleep Disorders (ICSD-3) criteria (Appendix B). If documentation of the IH diagnosis is unavailable in the screening window, diagnostic testing must be performed according to ICSD-3 criteria early in the screening window before starting the 10-day collection of the baselines for Sleep Diary, SIVAS and Mod-KSS (during 10 days before Visit 2). Diagnostic tests may include one of the following to confirm the diagnosis of IH:

    - Nocturnal polysomnogram (PSG) followed by a multiple sleep latency test (MSLT). The duration of the MSLT must be long enough to include at least 4 naps.
    - 24-hour PSG
    - Wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).

    Note: If a PSG/SMLT is needed, it should be scheduled as soon as possible to make sure it will be performed during the Screening Period before Visit 1A.
4. Subject demographics including date of birth, sex, race, and ethnicity.

5. Review of inclusion/exclusion criteria to determine study eligibility.
6. Record medical history including chronic conditions, relevant surgical procedures (with start date), medications, and history of alcohol and recreational drug use. This will include IH history, and usual time of going to sleep for the night and awakening time.
7. A complete physical examination.
8. Body weight, height, and Body Mass Index (BMI). BMI will be used to check the associated inclusion criterion (BMI must be $\leq$35 kg/m^2).
9. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
10. 12-lead electrocardiogram (ECG) after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
11. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting conditions. The fasting state (fasting yes/no) will be recorded. Clinical laboratory measurements may be repeated once at the discretion of the Investigator. Also, the glomerular filtration rate (GFR) will be calculated with the CKD-EPI 2009 method (Levey 2009) to evaluate the associated exclusion criterion (subjects with a GFR <60 mL/min/1.73 m^2 at Screening will be screen failed).
12. Urine screen or breath test for alcohol, and urine screen for drugs of abuse: Urine or breath will be tested for alcohol, and urine will be tested for drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone) and methylphenidate (MPH) at Screening (Visit 1) and at Visit 2. A urine dipstick will be used to screen for the presence of MPH in the urine. Subjects with a positive urine drug screen (eg, amphetamines, methylphenidate) may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required (test at Visit 2 needs to be negative). Subjects with a positive test at Screening may be rescreened (test at Visit 2 needs to be negative).
13. Serum β-human chorionic gonadotropin (β-hCG) pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.

14. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, "Baseline/Screening" version. Subjects with any history of attempted suicide (lifetime) or clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment at Screening, will be excluded from further participation in the study. Further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
15. Perform the Epworth Sleepiness Scale (ESS) assessment.
16. Review of concomitant medications, treatment and/or therapies.
17. Schedule Visit 1A and Visit 2. Visit 2 should be scheduled within the screening window, at a date that the Investigator will have thoroughly reviewed the results of all screening procedures and has confirmed all eligibility criteria.

    Subjects will also be instructed with the date on which to begin wash out of any medications prior to Visit 2. See Section 10 for the medications that are prohibited and their associated time frames, including the days that they are prohibited before Visit 2, ie, required washout days for subjects taking the medications.

9.1.1. Visit 1A ePRO training

Visit 1A will occur during the Screening Period, on Day -11 ±2 days, to allow for approximately 10 days between Visit 1A and Visit 2, to obtain baseline measurements of patient-reported assessments. If Visit 2 is unexpectedly delayed, it is acceptable that Visit 1A occurs earlier than planned relative to Visit 2 (ie, this is not a protocol deviation).

The following procedures will be performed at Visit 1A:

1. Review of inclusion/exclusion criteria for which data are available, to determine study eligibility.
2. Instruct/train subjects for the use of Electronic Patient-Reported Outcomes (ePRO) technology

Patient-reported assessments will be recorded with ePRO technology. The ePRO assessments during the study consist of the Sleep Diary, the Dosing Diary, the Sleep Inertia Visual Analog Scale (SIVAS), and the Modified Karolinska Sleepiness Scale (Mod-KSS). Subjects will complete the Sleep Diary, SIVAS and Mod-KSS daily during the 10 days prior to Visit 2 (during approximately the last 10 days of the Screening Period), to obtain pre-dose (baseline) values. Completion of the Dosing Diary will start after the administration of the first dose of study drug (evening of Visit 2) until the last administration of study drug (in the evening or morning before Visit 8), or Early Termination.

During Visit 1A, subjects will return to the clinic/site where the ePRO technology will be made available for access by the subjects. This will include providing a device or install an app on the subject's device, such as a smartphone or tablet. Subjects will enter their answers and scores for the ePRO assessments (Sleep Diary, Dosing Diary, SIVAS, and Mod-KSS) daily (once or twice per day as appropriate) on their electronic device, and will be prompted by the app during certain time windows of the day.

During Visit 1A, subjects will be instructed/trained by site staff on how to use the system before their first assessment that will start the next day, at home. Instructions will include the importance of completing the ePRO assessments daily within the time windows (ePRO compliance).

No other procedures are required at Visit 1A. However, if certain screening procedures are outstanding or need follow-up, they may be completed and/or discussed with the subjects at Visit 1A.

9.2. Open-Label Titration Period (Visit 2-6)

Subjects who meet the inclusion/exclusion criteria during Screening, will enter the Open-Label Titration Period (Visit 2-6, including days at home until Visit 7). The subjects will undergo the following procedures during these visits.

9.2.1. Visit 2

Visit 2 will occur no later than 35 days (the screening window) after starting screening procedures (Visit 1). The following procedures will be performed at Visit 2:

1. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility.
2. Update medical history.
3. A complete physical examination.
4. Body weight.
5. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
6. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.

7. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
8. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting conditions. The fasting state (fasting yes/no) will be recorded. Clinical laboratory measurements may be repeated once at the discretion of the Investigator.
9. Urine screen or breath test for alcohol and urine screen for drugs of abuse: Urine or breath will be tested for alcohol, and urine will be tested for drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone) and methylphenidate (MPH). A urine dipstick will be used to screen for the presence of MPH in the urine. Subjects will need to have a negative drug screen at Visit 2 to continue in the study.
10. Urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
11. Perform the ESS assessment.
12. Perform the Brain Fog Scale assessment.
13. Perform the Clinical Global Impression of Severity (CGI-S) assessment.
14. Perform the Patient Global Impression of Severity (PGI-S) assessment.
15. Perform the IH Severity Scale (IHSS) assessment.
16. Perform the Patient-Reported Outcomes Measurement Information System (PROMIS®-29) fatigue, social functioning, and depression assessments.
17. Perform the Patient-Reported Wakefulness Questionnaire (ZOGIM-A) assessment.
18. Perform the Pittsburgh Sleep Quality Index – Question #6 (PSQI-Q6) assessment.
19. Review the ePRO compliance with the subject, ie, completeness of Sleep Diary, SIVAS and Mod-KSS from the preceding 10 days (last 10 days of the Screening Period) for completeness. Determine subject eligibility for continuing in the study based on the following:

    - **Total Sleep Time (TST):** The average TST will be calculated from the last 7 days with complete daily data from the Sleep Diary needed to calculate the daily TST, or from the available days with complete data if <7 days are completed.

- **ePRO compliance:** Subjects that have been deficient in completing the Sleep Diary, SIVAS or Mod-KSS, will be excluded from further study participation, at the discretion of the Investigator. The minimum target is that subjects have completed all ePRO assessments for at least 6 out of the 10 days. (6 days with complete daily sets, evaluated separately for each of the Sleep Diary, SIVAS and Mod-KSS). Discretion by the Investigator may include judgement of emergencies, lost/malfunctioning electronic device, nearly complete assessments, etc. Site staff needs a strong commitment from the subjects to complete the ePRO assessments daily. Site staff needs to actively monitor the ePRO compliance throughout the study, and discuss issues and concerns with each subject on an ongoing basis.

20. Review of concomitant medications, treatment and/or therapies since last visit.
21. Assessment and review of Adverse Events (AEs), and the subject will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
22. Randomize the subjects (used to assign the dosing regimen) by assessing the IWRS, and provide subject with supply of study drug until the next visit (lowest dose of SDX as starting dose). Dose adjustments, if needed, will be performed at the scheduled visits (Visit 3 through Visit 5, each approximately 7 days apart) based on individual tolerability and effect.
23. Inform subjects that they will need to complete the Dosing Diary once or twice per day (as part of the ePRO assessments) and review the process as needed with the subject.
24. Schedule Visit 3.

If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.

See Section 9.10 for visit and assessment changes when a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions.

9.2.2. Visit 3 and Visit 4

Visit 3 will occur 7 ±3 days after Visit 2, and Visit 4 will occur 7 ±3 days after Visit 3. The following procedures will be performed at Visit 3 and Visit 4:

1. Record returned study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported

dosing information in their Dosing Diary.

2. Body weight
3. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
4. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
5. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
6. Perform a urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
7. Perform the ESS assessment.
8. Perform the Brain Fog Scale assessment.
9. Perform the CGI-S assessment.
10. Perform the PGI-S assessment.
11. Perform the IHSS assessment.
12. Perform the PROMIS®-29 fatigue, social functioning, and depression assessments.
13. Perform the ZOGIM-A assessment.
14. Review the ePRO compliance with the subject.
15. If needed, perform an adjustment of the dose based on individual tolerability and effect. Assess the IWRS as needed, and provide subject with supply of study drug until the next visit.

    If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.
16. Assessment and review of AEs, and instruct the subject to contact the study site for the reporting of AEs during the dosing periods at home.

17. Review of concomitant medications, treatment and/or therapies since last visit.
18. Schedule the next visit.

See Section 9.10 for visit and assessment changes when a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions.

9.2.3. Visit 5

Visit 5 will occur 7 ±3 days after Visit 4. The following procedures will be performed at Visit 5:

1. Record returned study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary.
2. Assessment and review of Adverse Events.
3. Review of concomitant medications, treatment and/or therapies.
4. Body weight
5. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
6. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
7. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
8. Perform a urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
9. Perform the ESS assessment.
10. Perform the Brain Fog Scale assessment.
11. Perform the CGI-S assessment.
12. Perform the PGI-S assessment.
13. Perform the IHSS assessment.

14. Perform the PROMIS®-29 fatigue, social functioning, and depression assessments.
15. Perform the ZOGIM-A assessment.
16. Perform the PSQI-Q6 assessment.
17. Review the ePRO compliance with the subject.
18. After Visit 5 and before Visit 7, subjects will visit the study site and will stay for a minimum of 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples (PK Visit). The PK Visit may coincide with Visit 6 or may occur on a separate day after Visit 5 and before Visit 7 (See Section 9.2.5).

    If the PK Visit is planned after Visit 5 and at or before Visit 6, study staff will schedule the PK Visit, and instruct subjects to bring unused drug supplies to the PK Visit.
19. Assessment and review of AEs, and instruct the subject to contact the study site for the reporting of AEs during the dosing periods at home.
20. Review of concomitant medications, treatment and/or therapies since last visit.
21. If needed, perform an adjustment of the dose based on individual tolerability and effect. Assess the IWRS as needed, and provide subject with supply of study drug until the next visit.

    If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.
22. Schedule Visit 6.

9.2.4. Visit 6

Visit 6 will occur 7 ±3 days after Visit 5. The following procedures will be performed at Visit 6:

1. Record returned study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary.
2. Body weight
3. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after

the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.

4. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
5. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
6. Perform a urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
7. Perform the ESS assessment.
8. Perform the Brain Fog Scale assessment.
9. Perform the CGI-S assessment.
10. Perform the PGI-S assessment.
11. Perform the IHSS assessment.
12. Perform the PROMIS®-29 fatigue, social functioning, and depression assessments.
13. Perform the ZOGIM-A assessment.
14. Review the ePRO compliance with the subject.
15. Assessment and review of AEs, and the subject will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
16. Review of concomitant medications, treatment and/or therapies since last visit.
17. After Visit 5 and before Visit 7, subjects will visit the study site and will stay for a minimum of 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples (PK Visit). The PK Visit may coincide with Visit 6 or may occur on a separate day after Visit 5 and before Visit 7 (See Section 9.2.5).

    - If the PK Visit was scheduled to coincide with Visit 6: Perform the procedures of the PK Visit outlined in Section 9.2.5.
    - If the PK Visit is scheduled after Visit 6 (and, as required, before Visit 7), study staff will schedule the PK Visit, and instruct subjects to bring unused drug

supplies to the PK Visit.

18. If needed, perform an adjustment of the dose based on individual tolerability and effect. It is the intention that the dose during the last week of the Titration Period (Visit 6 to Visit 7) is the same as during the previous week, although, mainly for safety reasons, it is at the Investigator's discretion to change the dose at Visit 6.

    Assess the IWRS as needed, and provide subject with supply of study drug until the next visit.

    If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.

19. Schedule Visit 7.

See Section 9.10 for visit and assessment changes when a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions.

9.2.5. Pharmacokinetics (PK) Visit

At least 12 subjects in each treatment regimen group (24 subjects in total) will visit the study site and will stay for a minimum 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples. See Section 1.1 for the Schedule of Events during the PK Visit.

The PK Visit may coincide with Visit 6 or may occur at a separate day after Visit 5 and before Visit 7, as follows:

PK Visit is scheduled to coincide with Visit 6: Subjects will visit the research clinic during the day of Visit 6 to complete all study procedures for Visit 6, and will stay overnight to start a 24-hour period for dosing and PK sample collections, starting at bedtime on the Visit 6 day and ending with the last PK sample collection 24 hours later (day after the Visit 6 day).

If possible, subjects will need to have received the same daily dose of study drug for at least 3 consecutive days immediately before the PK Visit. This dose is not necessarily the optimal dose.

Subjects will complete all procedures of Visit 6 (Section 9.2.4) and the procedures specific for the PK Visit listed below.

PK Visit is scheduled on a day different from Visit 6 (but after Visit 5 and before Visit 7, as required): Subjects will visit the research clinic for their scheduled PK Visit scheduled as follows:

- After the Visit 5 day and before the Visit 7 day.
- If possible, after subjects have received the same daily dose of study drug for at least 3 consecutive days immediately before the PK Visit.

If the PK Visit does not coincide with Visit 6, subjects will complete the following study procedures before starting the 24-hour period for dosing and PK sample collections:

1. Record remaining study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused (remaining) medication to the clinical site. Subjects will keep the remaining study drug, as appropriate (since they will continue at-home dosing after the PK Visit).
2. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
3. Assessment and review of AEs.
4. Review of concomitant medications, treatment and/or therapies since last visit.
5. Confirm that subjects are completing the Sleep Diary, Dosing Diary, SIVAS and Mod-KSS daily.
6. Confirm scheduling of the next scheduled visit.

Procedures specific for the PK Visit: The following PK-related procedures will be performed during the PK Visit (these are the same irrespective whether the PK Visit coincides with Visit 6 or occurs on a separate day between Visit 5 and Visit 7):

1. **Dose Administration:**
    - Subjects receiving the bid regimen will take the am dose at home, before visiting the study site.
    - The subject's evening (pm) and morning (am, next day) dose of study drug for subjects receiving the bid regimen, and the evening dose for subjects receiving the qd pm regimen, will be administered at the research clinic under the supervision of site staff. This is needed to control time of dosing and to collect for PK samples at the correct predose and postdose times.
    - If possible, the dose size administered during the PK Visit will be same dose

size that the subject has taken during the last 3 days before the PK Visit (before any dose adjustments). This dose is not necessarily the optimal dose.

- While at the study site, doses of study drug will be administered at the following times:
  - For subjects receiving the bid regimen: as close as possible to the subject's regular administration times of the pm and am doses, and maintaining as best as possible their usual interval between both doses. The objective is to capture PK exposure over a full 24 hours, divided over 2 doses (am and pm).
  - For subjects receiving the qd pm regimen, doses will be administered 24 hours (±10 minutes) apart, as close as possible to the subject's regular dose administration time. The objective is to capture PK exposure over a full 24 hours after 1 daily pm dose.
- Time of going to sleep and wake-up time, mealtimes, and times of dose administration will be as close as possible to the subject's regular times.
- Actual time of going to sleep and wake-up time, mealtimes, and times of dose administration, as well as the dose size will be recorded (Sleep Diary and Dosing Diary). Other assessments (SIVAS and Mod-KSS) will also be recorded.

2. **PK Sample Collections:** Subjects will have PK samples collected over a 24-hour period, at the following times.
   - For subjects receiving the qd pm regimen: 0 (predose), 1, 2, 4, 5, 6, 8, 10, 12, 16, and 24 hours after the pm dose. The 24-hour sample will be collected before administration of the next dose (administered on the day following PK Visit day).
   - For subjects receiving the bid regimen: 0 (predose), 1, 2, 4, 5, 6, 8, 10, and 12 hours after the pm dose (PK Visit day), and 0 (predose), 1, 2, 4, 5, 6, 8, 10, and 12 hours after the am dose (day after PK Visit day). The last sample after the pm dose will be collected before administration of the am dose; the last sample after the am dose will be collected before administration of the pm dose.
     Since the bid regimen may be different for different subjects, with the dosing interval between the pm and am doses different from 12 hours, the PK sampling times will need to be adjusted accordingly. Guidelines for individualization are listed in Section 1.1, will be included in the PK Manual, and may be discussed with the Sponsor for each subject.

- On the night of the PK Visit day, samples collected during the night (after the pm dose) will be collected under "sleep conditions" including the following: subjects will need to lay down all night except for bathroom visits, dim lights, quiet environment (no loud noises, no use of electronics, TV, etc) to mimic night conditions as much as possible.

- The blood PK samples will be collected at the nominal time points ±5 minutes.

9.3. Procedures Conducted by Subjects at Home

9.3.1. Dose Administration

While at home during the Titration Period and the Withdrawal Period, subjects will take study drug at the following times:

- Subjects receiving the qd pm regimen will take their dose of study drug daily just before going to sleep at night.
- Subjects receiving the bid regimen will take their dose of study drug daily shortly after awakening (am dose) at and just before going to sleep at night (pm dose).

Study drug may be taken with or without food.

Subjects who forgot to take their study drug at the specified times (shortly after awakening and/or just before going to sleep at night) may take it up to approximately 3 hours later; if more than approximately 3 hours have passed, they will skip the dose administration, and proceed to take study drug at the next scheduled time.

9.3.2. Patient-Reported Outcomes (PROs)

While at home during the 10 days before Visit 2 (during the last 10 days of the Screening Period), Titration Period (5 weeks) and Withdrawal Period (2 weeks), subjects will complete the following ePRO assessments daily, as follows:

- Sleep Diary: Subjects will keep a Sleep Diary (Appendix L) on a day-by-day basis throughout the study. The Sleep Diary includes questions about last night's sleep, morning wake-up, and daytime naps. The sleep diary should preferably be completed within 1 hour of awakening in the morning, and again at night just before going to sleep.
- SIVAS: Subjects will complete the SIVAS (Appendix K) daily at approximately 1 hour after awakening. The SIVAS is an assessment on how difficult it is to wake

up in the morning (Sleep Inertia).

- Mod-KSS: Subjects will complete the Mod-KSS (Appendix H) daily at approximately 1 hour after awakening and again, preferably shortly after 6 pm. Subjects will indicate daily which level best reflects their sleepiness experienced during the first hour after awakening and in late afternoon (from 5 pm to 6 pm).

9.3.3. Dosing Diary

- While at home from the administration of the first dose of study drug (Visit 2) until the last dose of study drug (in the evening or morning before Visit 8), subjects will complete the Dosing Diary once or twice per day. The Dosing Diary (Appendix M) consist of a recording of the dosing time, and whether the subject consumed a meal during ±1 hour around the dosing time (excluding small snacks such a candy bar). The Dosing Diary should be completed at night just after taking the evening dose by subjects receiving the qd pm dosing regimen; and in the evening and morning after taking the respective doses by subjects receiving the bid dosing regimen.

9.3.4. ePRO Compliance

Site staff needs a strong commitment from the subjects to complete the ePRO assessments daily (Sleep Diary, Dosing Diary, SIVAS and Mod-KSS). Site staff needs to actively monitor the ePRO Compliance throughout the study, and discuss issues and concerns with each subject on an ongoing basis (including contacting the subjects by phone, Email, or text).

The minimum ePRO Compliance target is that subjects complete all ePRO assessments for at least 60% of the time (ePRO Compliance), evaluated separately for each of the Sleep Diary, Dosing Diary, SIVAS and Mod-KSS, as follows:

- During the last 10 days of the Screening Period: Completion of all ePRO assessments for at least 6 out of the 10 days (6 days with complete daily sets, evaluated separately for each of the Sleep Diary, SIVAS and Mod-KSS).

- During the Titration Period: completion of all ePRO assessments for at least 4 days out of the 7 day intervals between visits (4 days with complete daily sets, evaluated separately for each of the Sleep Diary, Dosing Diary, SIVAS and Mod-KSS).

- During the Withdrawal Period: completion of all ePRO assessments for at least 4 days out of the first 7 day interval, and at least 4 days out of the second 7 day interval (4 days with complete daily sets for each of the 2 weeks between visits, evaluated separately for each of the Sleep Diary, Dosing Diary, SIVAS and Mod-KSS).

If visits are spaced apart differently (more or less days than listed above), the minimum ePRO compliance in terms of days with complete datasets, will be calculated based on a 60% compliance. The expectation is that most subjects do much better than 60%.

9.3.5. Drug Safety

If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.

9.4. Double-Blind Withdrawal Period (Visit 7)

Visit 7 will occur 7 ±3 days after Visit 6. Visit 7 is the end of the Titration Period: The final dose of open-label study drug in the Titration Period will be administered at home in the evening before the Visit 7 day for Treatment X (qd pm dosing regimen) and in the morning of the Visit 7 day for Treatment Y (bid dosing regimen).

Visit 7 is also the start of the Withdrawal Period: the first dose of double-blind drug in the Withdrawal Period will be administered at home in the evening of the Visit 7 day for all treatments.

The Double-Blind Withdrawal Period will consist of 2 weeks during which the subjects will receive the optimized dose (blinded SDX or matching placebo). The subjects will have clinic visits at the beginning and end of the period (Visits 7 and 8). At the start of the Withdrawal Period, subjects within each treatment group of the Titration Period will be randomized in a 2:1 ratio to SDX or placebo. This randomization will be stratified by optimized dose.

The following procedures will be performed at Visit 7:

1. Confirm the subject meets eligibility criteria for the withdrawal period.
    - Subjects demonstrate adequate compliance with dosing in the Titration Period. Adequate compliance in the Titration Period is defined as 80-100% based on study drug accountability since Visit 2. Subjects may also be withdrawn early (even if their numerical compliance in the Titration period is within 80-100%) at the discretion of the Investigator, if the Investigator expects poor compliance in the Withdrawal Period (for example, when subjects lost or failed to return unused study drug on multiple occasions during the Titration period).
    - No ongoing AEs occur due to SDX treatment that would require dose adjustment or early discontinuation during the Withdrawal Period.

- Subjects must have a decrease of their ESS score of at least 2 points at Visit 7 compared to titration baseline (Visit 2).

2. Record returned study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary.
3. Body weight
4. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
5. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
6. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
7. Perform a urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
8. Perform the ESS assessment.
9. Perform the Brain Fog Scale assessment.
10. Perform the CGI-S assessment.
11. Perform the PGI-S assessment.
12. Perform the IHSS assessment.
13. Perform the PROMIS®-29 fatigue, social functioning, and depression assessments.
14. Perform the ZOGIM-A assessment.
15. Perform the PSQI-Q6 assessment.
16. Review the ePRO compliance.
17. Assessment and review of AEs, and the subject will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
18. Review of concomitant medications, treatment and/or therapies since last visit.

19. Establish each subject's optimized dose of SDX. Randomize subject to one of the blinded treatments (SDX or placebo) according to the randomization schedule, by assessing the IWRS. Provide subject with supply of study drug until the next visit (drug supply for 2 weeks).

    Subjects will continue receiving their optimized dose daily throughout the Withdrawal Period. The individually established optimized dose may only be changed by the Investigator if needed for reasons of intolerability. Subjects will receive the blinded optimized dose of study drug according to the dosing regimen (either qd pm or bid) determined earlier in the study.

    If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their dose of study drug may be adjusted before the next scheduled visit. Unscheduled visits between the scheduled visits are allowed as needed, at the discretion of the Investigator.

20. Schedule Visit 8.

See Section 9.10 for visit and assessment changes when a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions.

9.5. End of Treatment (Visit 8)

Visit 8 will occur 14 ±3 days after Visit 7. The final dose of study drug will be administered at home in the evening before the Visit 8 day for Treatments A and B (qd pm dosing regimen) and in the morning of the Visit 8 day for Treatments C and D (bid dosing regimen).

The following procedures will be performed during the end of treatment visit (Visit 8):

1. Record returned of study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary.
2. A complete physical examination.
3. Body weight
4. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
5. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the

repeated ECG will be recorded.

6. Perform the C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
7. Perform the ESS assessment.
8. Perform the Brain Fog Scale assessment.
9. Perform the CGI-S assessment.
10. Perform the PGI-S assessment.
11. Perform the IHSS assessment.
12. Perform the PROMIS®-29 fatigue, social functioning, and depression assessments.
13. Perform the ZOGIM-A assessment.
14. Perform the PSQI-Q6 assessment.
15. Review the ePRO compliance with the subject.
16. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting conditions. The fasting state (fasting yes/no) will be recorded. Clinical laboratory measurements may be repeated once at the discretion of the Investigator.
17. Urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
18. Review of concomitant medications, treatment and/or therapies since last visit.
19. Assessment and review of AEs.
20. Schedule the Follow-Up Phone Call.

9.6. Early Termination Visit

Early Termination (ET) from the study is defined as withdrawal during the Open-Label Titration Period or Double-Blind Withdrawal Period after at least one dose of study drug is administered. For subjects who withdraw early from the study, the Investigator should make every effort to perform all ET procedures before discharging the subject from the research clinic when the ET Visit coincides with another study visit, or during the ET Visit scheduled on a different day than other study visits. At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day (as part of another study visit) do not need to be repeated.

The following procedures will be performed at the ET visit:

1. Record returned of study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary.
2. A complete physical examination.
3. Body weight.
4. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.
5. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
6. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting or non-fasting conditions. The fasting state (fasting yes/no) will be recorded.
7. Urine pregnancy test for all female subjects of childbearing potential.
8. Assessment of the Columbia Suicide Severity Rating Scale (C-SSRS), "Since Last Visit" version. If a subject has clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
9. Review the ePRO compliance with the subject.
10. Perform the PSQI-Q6 assessment.
11. Review of concomitant medications, treatment and/or therapies since last visit.
12. Assessment and review of AEs.

Subjects who withdraw early from the study and complete the above ET procedures will not need a Follow-Up Phone Call. Therefore, the ET Visit is the EOS for these subjects.

9.7. Follow-Up Phone Call

Subjects who complete all periods of the study from the Open-Label Titration Period through the Double-Blind Withdrawal Period will have a phone call in 7 ±3 days after the administration of the last dose of study drug (7 ±3 days after Visit 8).

The following procedures will be completed during the visit:

1. Review of concomitant medications, treatment and/or therapies since last visit.
2. Assessment and review of AEs.

The Follow-Up Phone Call is the End-of-Study (EOS) for subjects who complete all periods of the study.

9.8. End of Study (EOS)

The EOS is either the Follow-Up Phone Call for subjects who complete all periods of the study or the Early Termination Visit for subjects who withdraw early from the study.

9.9. Unscheduled Visits

At the discretion of the Investigator, subjects may be asked to come to the clinical site for an unscheduled visit. Unscheduled visits can occur at any time between visits. Examples of reasons to conduct an unscheduled visit:

- If subjects experience an AE during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, further in-person medical evaluation and review is needed. At the discretion of the Investigator, their SDX dose may be adjusted before the next scheduled visit.
- If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, then sites will be instructed to collect data for select safety assessments (vital signs, weight, ECG, clinical laboratory tests, physical examinations, C-SSRS) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit (Section 9.10).

The following procedures will occur at the Unscheduled Visit:

1. Record returned or remaining study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused (remaining) medication to the clinical site. Review dosing compliance based on drug accountability and patient-reported dosing information in their Dosing Diary. If treatment continues after the unscheduled visit, subjects will keep the remaining study drug, or will be dispensed new study drug as appropriate (such as in case a dose change is needed).
2. Review the ePRO compliance with the subject.
3. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, out-

of-range vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded.

4. Assessment and review of AEs.
5. Review of concomitant medications, treatment and/or therapies since last visit.
6. Confirm scheduling of the next scheduled visit.

The following procedures will occur at the Unscheduled Visit, each at the discretion of the Investigator:

Evaluations for safety, as needed (for example, to evaluate and review Adverse Events):

1. Physical examination
2. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
3. C-SSRS, "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
4. Clinical laboratory assessments will be obtained under fasting or non-fasting conditions. The fasting state (fasting yes/no) will be recorded.

Evaluations for efficacy, as needed (for example, to evaluate a change in dose of study drug):

1. Perform the ESS assessment.
2. Perform the PGI-S assessment.

If a subject meets withdrawal criteria during the Unscheduled Visit, the subject will be withdrawn, and Early Termination procedures will be completed (see Section 9.6). At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the Unscheduled Visit do not need to be repeated.

9.10. Visit and Assessment Changes Due to COVID-19

Due to the COVID-19 public health emergency and in alignment with the Food and Drug Administration (FDA) Guidance for Industry, Investigators, and Institutional Review Boards entitled: FDA Guidance on Conduct of Clinical Trials of Medical Products during

COVID-19 Public Health Emergency (March 2020; updated August 30, 2021), alternative measures will be implemented for some subjects and/or sites participating in the study. Measures will be implemented on an "as needed" basis, to maintain trial continuity, sustain subjects' access to study drug and ensure the continued safety of subjects and the integrity of the study data. Where it is possible, the study will be conducted in accordance with the protocol. However, for some study subjects and sites, the COVID-19 public health emergency and resulting "stay at home" orders, site closures, and travel limitations may lead to difficulties in meeting protocol-specified procedures, including on-site delivery of investigational product and adhering to protocol-mandated on-site visits and laboratory/diagnostic testing for the study. In these circumstances, alternative measures will be employed and documented as protocol deviations that will be summarized within the CSR. These alternative measures are intended to remain in effect only for the duration of the public health emergency related to COVID-19 and are applied only if an on-site study visit cannot occur. The measures include the delivery of study drug directly to subject's residence and replacing on-site study visits with remote study visits, which may include:

- Adaptation of efficacy assessments
- Alternative methods for safety assessments

A listing of all subjects affected by the COVID-19 related study disruption by subject number and by investigational site, and a description of how the individual's participation was altered will be generated. Specifically, the listing will include, but is not limited to, the following:

- Subjects who had on-site visits converted into remote visits
- Subjects who had visits and/or assessments not performed/missing along with the reason.
- Subjects who had safety and efficacy data collected out of window

All the above study changes will be captured as protocol deviations. Additionally, these data will be captured within comment fields in the EDC.

If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, then sites will be instructed to collect data for select safety assessments (vital signs, weight, ECG, clinical laboratory tests, physical examinations, C-SSRS) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit (Appendix A). These assessments will be mapped to the nearest scheduled visit. Changes in scheduled visits and corresponding assessments due to COVID-19 restrictions will be captured in the eCRF. Instructions will be included in the Site Operations Manual for capturing visits and/or assessments that were missed (not performed), delayed, or performed remotely. The following visit and assessment changes will be included in

submission datasets:

- All on-site visits that were converted to remote visits due to COVID-19 restrictions will be flagged. This information will be captured in the eCRF and protocol deviation log.
- Missed visits and assessments are flagged if the "not done" field is indicated and the comment field indicates "COVID-19".

Assessments that do not require the subject's presence at the site will be collected by phone at the scheduled visit times. If needed, alternate measures to dispense study drug to the subjects during their COVID-19 isolation period will be implemented (eg, study drug directly delivered to the subject's residence or dispensed to another family member).

10. CONCOMITANT MEDICATION RESTRICTIONS

Subjects will adhere to the following medication restrictions during the study.

Medications to treat IH and all medications that can affect wakefulness and sleep are prohibited during the trial, including the following:

- Wake-Promoting Agents (WPA) including modafinil, armodafinil, solriamfetol, and pitolisant.
- CNS Stimulants (amphetamine, methylphenidate, methamphetamine, pseudoephedrine).
- CNS sedating and/or anti-insomnia agents, including but not limited to:
  - Sodium oxybate (Xyrem®) and calcium, magnesium, potassium & sodium oxybates (Xywav®)
  - Benzodiazepine hypnotics (benzodiazepine receptor agonists [BZRAs]: estazolam, flurazepam, temazepam, triazolam, oxazepam, and quazepam)
  - Nonbenzodiazepine BZRAs (eszopiclone, zaleplon, and zolpidem)
  - Orexin receptor antagonist insomnia treatments (daridorexant, suvorexant, and lemborexant)
  - Sedating anxiolytics (midazolam, lorazepam, chlordiazepoxide, diazepam, alprazolam, flunitrazepam)
  - Sedating antidepressants (Appendix P)
    Note: Patients may be switched from a sedating to a non-sedating antidepressant as long as the switch occurs at least 14 days before Visit 2.
  - Sedative antihistamines (diphenhydramine, dimenhydrinate, brompheniramine)
  - Neuroleptics (haloperidol, trifluoperazine, fluphenazine. thioridazine, chlorpromazine, thiothixene, clozapine, olanzapine, paliperidone, risperidone, aripiprazole, asenapine, cariprazine, lurasidone, quetiapine, ziprasidone)
  - Opioids (oxycodone, hydrocodone, morphine, methadone)

- Barbiturates (pentobarbital, phenobarbital, amobarbital, butalbital)
- Gamma-hydroxybutyrate (GHB, oxybate) dehydrogenase inhibitors (anticonvulsants valproate, ethosuximide, phenytoin)
- Dopamine antagonist antiemetics (chlorpromazine, metoclopramide, promethazine, paliperidone, risperidone, quetiapine, clozapine; except domperidone which is allowed)
- Melatonin and melatonin receptor agonists (ramelteon)
- Clonidine
- Myorelaxants/antispasmodics (baclofen, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine)
- Any other medication that may cause sedation.

The following medications are also prohibited with methylphenidate treatment due to possible pharmacodynamic drug-drug interactions:

- Monoamine oxidase inhibitors (MAOIs: rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine)
- Neuroleptics (see list above; excluded also because of their sedating effects)
- Coumarin anticoagulants (warfarin, acenocoumarol, phenprocoumon)
- Anticonvulsants (phenobarbital, diphenylhydantoin, primidone)
- Halogenated anesthetics
- Antihypertensive drugs
- Phenylbutazone

The prohibited medications listed are examples; this is not an exhaustive list. The Medical Monitor should be contacted for any questions or when in doubt for subject study eligibility.

If a subject has received any of the therapies listed above, a washout-period of at least 14 days, or equivalent to 5 half-lives of the drug, whichever is longer (and 30 days for sedating antidepressants; 14 days for CNS stimulants), is required prior to the first dose of study drug. Subjects must abstain from these medications during the study until the Follow-Up Phone Call or Early Termination Visit.

Patients may be switched from a sedating to a non-sedating antidepressant as long as the switch occurs at least 14 days before Visit 2.

NOTE: Subjects will be notified by site staff to exercise caution in performing daily tasks including driving and using machinery, as their daytime sleepiness may get worse after washing out WPAs or stimulants.

11. INVESTIGATIONAL PRODUCT

11.1. Active Pharmaceutical Ingredients

The chemical name of SDX Cl is 3-(((S)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((R)-2-((R)-2-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridine-1-ium chloride (single d-methylphenidate molecule covalently attached via a carbamate bond to a methylene oxide linker which in turn is connected to the nitrogen of the pyridine ring of a nicotinoyl-serine moiety).

11.2. Clinical Trial Material

The following daily doses will be administered orally during the Open-Label Titration Period and the Double-Blind Withdrawal Period:

- 80 mg/day SDX, orally
- 160 mg/day SDX, orally
- 240 mg/day SDX, orally
- 320 mg/day SDX, orally
- Placebo, orally (Withdrawal Period only)

The SDX amount and the total equivalent amount of d-MPH for each dose, are listed in the following table:

SDX Dose (mg/day)	SDX Cl Dose (mg/day)	Equimolar d-MPH HCl Dose (mg)
80	85.7	43.1
160	171.3	86.2
240	257.0	129.4
320	342.7	172.5

Doses of study drug will be administered orally as capsules, either qd pm or bid (Section 8). Subjects receiving the qd pm regimen will take the total daily dose (2 capsules) at night; subjects receiving the bid regimen will take half the daily dose (1 capsule) in the morning and half the daily dose (1 capsule) in the evening.

All study drugs will be taken with approximately 240 mL (8 oz) water. Study drug may be taken with or without food. The capsules must be swallowed whole without cutting, crushing, chewing, or opening.

The placebo capsules will be identical in appearance as for active drug, and the same number of capsules will be taken as for the same dose of active drug.

11.3. Packaging and Labeling

SDX capsules for the Open-Label Titration Period and the SDX and placebo capsules for the Double-Blind Withdrawal Period will be packaged and labeled according to the appropriate FDA regulations.

11.3.1. Open-Label Titration Period

In the Open-Label Titration Period, drug supplies will be assigned to individual subjects according to the randomization between the 2 dosing regimens (qd pm or bid). This assignment will not be blinded. Subjects randomized to one the 2 dosing regimens in the beginning of the Titration Period, will receive study drug according to the same assignment (qd pm or bid) for the remainder of the study. Titration of the dose towards an optimal dose in the Titration Period will lead to changes of the SDX dose over time, and drug supply assignments will therefore adjust accordingly.

The open-label study medication used in the Titration Period will consist of bottles with 20 capsules that will be packaged and labeled appropriately. Subjects will receive study drug supplies at each visit with enough study drug until the next visit, with extra capsules to allow for variations in the interval between visits.

11.3.2. Double-Blind Withdrawal Period

In the Double-Blind Withdrawal Period, within each dosing regimen group (qd pm or bid), drug supplies will be assigned to individual subjects according to the randomization between active drug (SDX) and placebo. This assignment will be blinded. Subjects will receive their individual optimized daily dose during the Withdrawal Period.

To maintain blinding (SDX vs placebo) in the Withdrawal Period, the study medication for the Withdrawal Period will be numbered (instead of labeled as active drug or placebo). Management of this numbering system, distribution of the numbered bottles across the clinical sites, and the assignment of drug supplies to the subjects will be managed by a computerized Interactive Web Response System (IWRS). At the time of randomization, site staff will contact the IWRS with the appropriate subject information including subject identification, gender, and optimized dose level. Based on this information, the IWRS will provide the drug supply number that will link the subject's randomization code to the treatment according to the Withdrawal Period randomization scheme. The drug supply number will correspond with one of the drug supply units available at the study site (part of the drug supplies previously shipped to the site). Site staff will dispense study drug with the assigned number to the subjects.

The blinded study medication used in the Withdrawal Period will consist of 2 bottles with

20 capsules that will be packaged and labeled appropriately. Subjects will receive study drug supplies with enough study drug to cover the duration of the Withdrawal Period, with extra capsules to allow for variations in the interval between visits.

Specific directions for using the IWRS and drug supply dispensing will be included in the Pharmacy Manual.

11.4. Dispensing Procedures

11.4.1. Open-Label Titration Period

During the Titration Period, subjects will receive daily doses of SDX. At the start of the Titration Period, subjects will be randomized to one of the 2 dosing regimens (qd pm or bid). The randomization will be stratified by gender.

The subject's treatment will be titrated (change of dose as needed) to an optimal daily dose of SDX starting with the lowest dose, based on individual tolerability and effect.

One unblinded bottle with 20 capsules will be dispensed at each visit as follows:

- **Visit 2:** At Visit 2, subjects will be dispensed SDX (starting dose), with instructions to take drug per the randomization schedule for the Titration period (qd pm or bid).
- **Visit 3:** Subjects will return to the research clinic (7 ±3 days after the previous visit) with unused study drug and will be dispensed SDX: the same or increased dose, to be taken qd pm or bid per randomization schedule for the Titration period.
- **Visit 4:** Subjects will return to the research clinic (7 ±3 days after the previous visit) with unused study drug and will be dispensed SDX: the same, decreased or increased dose, to be taken qd pm or bid per randomization schedule for the Titration period.
- **Visit 5:** Subjects will return to the research clinic (7 ±3 days after the previous visit) with unused study drug and will be dispensed SDX: the same, decreased or increased dose, to be taken qd pm or bid per randomization schedule for the Titration period.
- **Visit 6:** Subjects will return to the research clinic (7 ±3 days after the previous visit) with unused study drug and will be dispensed SDX to be taken qd pm or bid per randomization schedule for the Titration period. It is the intention that the dose during the last week of the Titration Period (Visit 6 to Visit 7) is the same as during the previous week, although, mainly for safety reasons, it is at the Investigator's discretion to change the dose.

Detailed dispensing instructions will be provided in the Pharmacy Manual.

11.4.2. Double-Blind Withdrawal Period

During the Withdrawal Period, subjects will receive daily doses of SDX or matching placebo. The dose level for each subject will be the optimized dose determined individually at the end of the Titration Period. At the start of the Withdrawal Period, subjects within each treatment group (qd pm or bid) of the Titration Period will be randomized in a 2:1 ratio to SDX or placebo. This randomization will be stratified by optimized dose.

Two blinded bottles with 20 capsules each (SDX capsules or matching placebo capsules) will be dispensed at each visit as follows:

- **Visit 7:** Subjects will return to the research clinic for Visit 7 (7 ±3 days after the previous visit).

  Visit 7 is the end of the Titration Period. The final dose of open-label study drug in the Titration Period will be administered at home in the evening before the Visit 7 day for Treatment X (qd pm dosing regimen) and in the morning of the Visit 7 day for Treatment Y (bid dosing regimen). Subjects will return unused study drug from the last week of the Titration period at Visit 7.

  Visit 7 is also the start of the Withdrawal Period. Subjects will be dispensed blinded study drug (SDX or Placebo) according to the randomization schedule for the Withdrawal Period. The daily dose will be the individual optimized dose determined in the Titration Period, and the dosing regimen (qd pm or bid) will be the same as in the Titration Period. The first dose of double-blind drug in the Withdrawal Period will be administered at home in the evening of the Visit 7 day for all treatments.

- **Visit 8:** Subjects will return to the research clinic (14 ±3 days after the previous visit) with unused study drug. The final dose of study drug will be administered at home in the evening before the Visit 8 day for Treatments A and B (qd pm dosing regimen) and in the morning of the Visit 8 day for Treatments C and D (bid dosing regimen).

If subjects report lost study drug during the at-home dosing periods, they will be instructed to contact the study site as soon as possible after the loss. Lost drug supply may be replaced with the appropriate new bottle after the Investigator or designee contacts the IWRS.

The Investigator will not supply study drug to anyone other than those named as sub-investigators on FDA Form 1572, designated site staff, and subjects in the study.

11.5. Storage of Study Drug

Study drug will be stored at controlled room temperature 15°-25°C (59°-77°F) with excursions allowed from 5° up to 40°C (41°-104°F) as long as they do not last for more than 24 hours in total (total allowable cumulative exposure).. Study drug will be stored in a safe, secure area with limited, controlled access in accordance with all local, state, and federal regulations. Investigational products must not be frozen. The Investigator will ensure that adequate precautions are taken, including storage of the study drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the CRO and the Sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product.

11.6. Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject, in both the Open-Label Titration Period and the Double-Blind Withdrawal Period, will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed will be recorded on the Investigational Drug Accountability Record. The study monitor will verify and reconcile these documents throughout the course of the study.

12. DIAGNOSIS (IDIOPATHIC HYPERSOMNIA)

At Screening, eligible subjects must meet all inclusion criteria for a primary diagnosis of IH according to the ICSD-3 criteria (Appendix B) (Sateia 2014, AASM 2014). Before enrollment of a subject into the Titration Period of the study, the documentation that meets all ICSD-3 diagnostic criteria needs to be available for that subject. If documentation of IH diagnosis is unavailable in the screening window, diagnostic testing must be performed early in the screening window before starting the 10-day collection of the baselines for Sleep Diary, SIVAS and Mod-KSS (1 week before Visit 2). Diagnostic tests may include one of the following to confirm the diagnosis of IH:

- Nocturnal polysomnogram (PSG) followed by a multiple sleep latency test (MSLT). The duration of the MSLT must be long enough to include at least 4 naps.
- 24-hour PSG

- Wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).

Making a diagnosis of IH requires careful exclusion of other causes of daytime sleepiness such as insufficient sleep (sleep deprivation), narcolepsy, disturbed nocturnal sleep, insomnia, circadian rhythm disorders, sleep-related breathing (sleep apnea) disorders or other medical issues.

12.1. Polysomnography (PSG)

A diagnostic PSG, also known as an in-lab sleep study, is an overnight recording of patterns and behaviors associated with sleep. It is performed to determine nocturnal sleep quality and duration, based on what stages of sleep an individual achieves and whether any sleep-related abnormalities are present. A PSG monitors brain waves (electroencephalogram, EEG), heart rhythm (ECG) and breathing during nocturnal sleep, and also tracks eye (electro-oculogram, EOG), leg and arm movements (electromyogram, EMG), and blood oxygen levels.

A PSG is required prior to the MSLT to objectively characterize preceding sleep and uncover potential causes of sleep fragmentation. The PSG must have confirmed at least 6 hours of sleep for the MSLT results to be considered in diagnosing EDS. Typical PSG findings in IH include shortened sleep latency, increased sleep efficiency (often >90%), and increased slow wave sleep, although these are nonspecific, and an MSLT is needed for a proper IH diagnosis.

12.2. Multiple Sleep Latency Test (MSLT)

The MSLT checks for EDS by measuring how quickly subjects fall asleep in a quiet environment during the day. Also known as a daytime nap study, the MSLT is used in the differential diagnosis of narcolepsy and IH.

The MSLT is a full-day test that consists of 4-5 scheduled and monitored naps separated by two-hour breaks. This test is almost always done following a PSG. During each nap trial, subjects will lie quietly in bed and try to go to sleep. Once the lights go off, the test will measure how long it takes to fall asleep (sleep latency). Subjects will be awakened after sleeping 15 minutes. If subjects do not fall asleep within 20 minutes, the MSLT will end. Between naps, subjects should be out of bed and be prevented from sleeping.

The test is based on the idea that subjects fall asleep in a shorter amount of time as their feeling of sleepiness increases. The study also measures how quickly and how often subjects enter the REM stage of sleep.

A typical montage to collect the needed physiologic measures (including brain waves, heartbeats, eye and chin movements) for an MSLT includes central and occipital EEG, left and right EOG, chin EMG, and ECG. Since rapid eye movement (REM) sleep is a critical measure, the addition of upper and lower EOG is recommended. It is optional to add oximetry, airflow detection, respiratory effort, and limb EMG.

A positive MSLT is obtained when the subject falls asleep with a mean sleep latency ≤8 minutes in the naps, and had no more than 1 nap (for IH diagnosis) or at least 2 naps (for narcolepsy diagnosis) where REM sleep was reached ("Sleep Onset REM Periods" (SOREMPs)). In normal healthy adults, REM sleep is reached after about 90 minutes of sleep onset. In contrast, SOREMPs in IH and narcolepsy occur within 15 minutes of sleep onset.

13. SAFETY ASSESSMENTS

13.1. Medical History

A complete medical history will be obtained at the Screening Visit including the recording of demographic data (date of birth, sex, age, race, ethnicity), collection of previous surgeries, medications and chronic conditions, past or present illnesses or dysfunctions, substance/drug abuse, and history of allergies or idiosyncratic responses to drugs. Medical history (changes from screening) will be updated at subsequent visits after the Screening Period.

13.2. Physical Examination

A complete physical examination including the measurement of body weight will be completed for all subjects at Screening, Visit 2, Visit 8, and the Early Termination Visit (if possible). The complete physical examination will include a review of the subject's general appearance, skin, head and neck (eyes, ears, nose, mouth, and throat), lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, lungs, abdomen and a brief examination of the neurological system.

All or part of a physical examination can be performed for investigation of a possible or established Adverse Event.

13.3. Body Weight, Height, and Body Mass Index (BMI)

The measurement of body weight will be obtained at Screening, at Visits 2-8, and at the ET visit (if possible). Height and BMI will be obtained at the Screening visit only.

Height will be recorded in centimeters (cm) using a stadiometer with the subject's shoes removed. Body weight will be measured in kilograms (kg) using a calibrated scale; subjects

will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.

13.4. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS, Appendix O) is a brief questionnaire that provides for the identification, quantification and standardized assessment of the occurrences and severity of suicidal ideation and behavior (see http://cssrs.columbia.edu). The typical administration time is a few minutes.

C-SSRS assessments will be performed by a trained rater at the following visits:

- Screening (Visit 1): The "Baseline/Screening" version of the C-SSRS (adult version) will be assessed.
    - Suicidal ideation will be assessed for lifetime and over the past 12 months.
    - Suicidal behavior will be assessed for lifetime and over the past 5 years.
- Visits 2-8, and ET (if possible): The "Since Last Visit" version of the C-SSRS (adult version) will be assessed.

Subjects with a history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or before the last dose of study drug, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

13.5. Vital Signs

Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Vital signs will be collected once at each visit according to Section 1, with repeats as defined below.

13.5.1. Abnormal Vital Signs

Vital sign measurements will be obtained as a single measurement after the subject has been sitting for a minimum of 3 minutes. To ensure accuracy, abnormal (out-of-range) vital signs will be repeated once, at least 2 minutes after an abnormal finding, in which case only the repeated measurement will be recorded. Abnormal Vital Signs for the purpose of repeating the measurement are defined as follows:

- Pulse rate outside the range of 60-100 beats per minute
- Blood pressure (BP) outside of the range of 90-120 mmHg for systolic BP, or 60-

80 mmHg for diastolic BP.

- Oral temperature outside of the range of 97.8-99.1°F.
- Respiratory rate outside the range of 12-20 breaths per minute.

13.5.2. Critical Vital Signs (Heart Rate and Blood Pressure)

If the repeated (second) value according to Section 15.5.1 for pulse rate or systolic/diastolic blood pressure exceeds the Critical Vital Sign threshold, a third measurement will be obtained approximately 30 minutes after the second measurement (after the subject has been sitting for a minimum of 3 minutes). The objective of the replicate measurements approximately 30 minutes apart is to identify a sustained elevation of the heart rate or blood pressure (and exclude a spurious and/or short increase).

The Critical Vital Sign thresholds are defined as follows:

- Pulse rate >150 beats per minute (defined as tachycardia)
- Systolic BP >160 mmHg.
- Diastolic BP >95 mmHg.

If the third measurement exceeds the Critical Vital Sign threshold, the subject's dose of study drug will be decreased and may not exceed the new dose level for the reminder of the trial. The critical finding will count towards the criteria to limit the highest dose in all subjects of the relevant dosing regimen cohort and the evaluation for a potential early termination of the relevant dosing regimen cohort (see Section 6.4). In addition, the critical finding may be recorded as an Adverse Event (according the CTCAE criteria, Section 19.1) and, at the discretion of the Investigator, study drug may be withdrawn and the subject may be terminated early from the study.

Note: For the safety of the subject, it is at the Investigator's discretion to decrease the subject's dose of study drug when clinically significant increases of heart rate or blood pressure are observed, even if they did not exceed the Critical Vital Sign thresholds.

13.5.3. Instructions/Preparations for Vital Sign Measurements

The instructions as based on the guidelines of the American Heart Association (AHA) for BP measurements in patients, in the office setting (Muntner 2019).

1. The subject should avoid caffeine, exercise, and smoking for at least 30 minutes before the measurement.
2. Ensure that the subject has emptied his/her bladder.

3. Have the subject relax, sitting in a chair with feet flat on floor (legs uncrossed) and back supported. The patient should be seated for approximately 3 minutes without talking or moving around before recording the measurement.
4. Neither the subject nor the clinic staff member taking the measurements should talk during the rest period or during the measurement, except when needed to provide/follow verbal instructions.
5. Remove clothing covering the location of the cuff placement. Shirtsleeves should not be rolled up (may create a tourniquet effect).
6. Use an appropriate size cuff. The most frequent error is "miscuffing" ("undercuffing" large arms in particular).
7. Support the subject's arm (eg, resting on a table) at heart level. The subject should not be holding his/her arm (isometric exercise increases BP levels).
8. Use an upper-arm cuff BP measurement device that has been validated and periodically calibrated.

13.6. 12-Lead Electrocardiogram

A 12-lead ECG will be obtained after the subject has been in a supine position for a minimum of 3 minutes. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded. ECGs will be obtained during visits as listed in Section 1.

The following ECG parameters will be recorded:

- Heart Rate (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT interval (msec)
- QTcF: QT interval corrected for heart rate with Fridericia's formula (msec)
- QTcB: QT interval corrected for heart rate with Bazett's formula (msec)
- RR Interval (msec)
- ECG Evaluation (performed at the clinical site): one of the following: Normal; Abnormal, not clinically significant; Abnormal, clinically significant. If Abnormal, a specific description of the abnormality in the ECG.

The numerical ECG parameters will be recorded from the ECG instrument, ECG printout, or calculated, as appropriate.

13.7. Clinical Laboratory Measurements

All clinical laboratory samples will be sent to a central laboratory for analysis. Up to

approximately 40 mL of blood will be collected for clinical chemistries, hematology, and pregnancy test (if applicable) from each subject during the study. Clinical Laboratory Measurements will be performed according to Section 1. Clinical Laboratory Measurements may be repeated once at the discretion of the Investigator.

All clinical laboratory samples will be collected under fasting conditions, except for the samples collected at Unscheduled Visits and at the Early Termination Visit, which may be collected under fasting or non-fasting conditions. Fasting is defined as no food or drinks (except water) for 8 hours. The fasting state (fasting yes/no) will be recorded to correctly interpret the results of the clinical laboratory results. A non-fasting state when fasting is required will not be recorded as a protocol deviation.

The Clinical Laboratory Measurements will consist of the following:

Laboratory Test	**Parameters**
Hematology	• red blood cell count • white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) • hemoglobin • hematocrit and platelets
Urinalysis	• microanalysis for specific gravity • pH • protein • glucose • ketones • blood • nitrites • leukocytes • If positive for blood, protein or nitrites, a microscopic examination will be performed.
Serum Chemistry	• aspartate aminotransferase (AST) • alanine aminotransferase (ALT) • albumin, alkaline phosphatase • bicarbonate • total bilirubin • blood urea nitrogen • phosphorus (inorganic) • calcium • chloride • creatine phosphokinase • creatinine • gamma glutamyl transferase

Laboratory Test	Parameters
	• glucose • lactate dehydrogenase • potassium • sodium • total protein • thyroid stimulating hormone (TSH). TSH will be measured at Screening only (to evaluate the exclusion criterion for subjects with uncontrolled thyroid disease • uric acid
Screen for Alcohol	• alcohol: urine test or breathalyzer
Urine Drug of Abuse Screen	• drugs of abuse (amphetamine, barbiturates, benzodiazepines, psychoactive cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, methamphetamines, MDMA, and oxycodone)
Urine MPH Screen	• methylphenidate: urine dipstick

13.8. Pregnancy Test

Pregnancy Tests: will be performed for all female subjects of childbearing potential. A serum β-hCG and urine pregnancy test will be performed according to Section 1. A positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. A positive urine pregnancy test will be confirmed with a serum β-hCG pregnancy test.

13.9. Adverse Event Assessments

Adverse Events will be assessed and recorded following enrollment (signing of consent) and ending with the Follow-Up Phone Call or Early Termination visit. Definitions and details of AE reporting and documentation are listed in Section 19.

13.10. Sleep Quality Assessments

The sleep quality will be rated using question #6 of the Pittsburgh Sleep Quality Index (PSQI) (Buysse 1989): "During the past week, how would you rate your sleep quality overall?" with responses of 0 = very good to 3 = very bad (Appendix N). The PSQI is a validated patient-reported global measure of nocturnal sleep disturbance that has been used in clinical trials in a variety of diseases. Question #6 of the PSQI (PSQI-Q6) has also been used to evaluate nocturnal sleep quality in patients with narcolepsy treated with sodium oxybate, modafinil, and their combination (Dauvilliers 2017).

14. EFFICACY ASSESSMENTS

The following efficacy questionnaires/rating scales will be used during both the Open-Label Titration Period and the Double-Blind Withdrawal Period to assess the changes in IH severity from week to week (Section 1).

14.1. Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) (Johns 1991; Appendix C) is a patient-administered questionnaire to measure a subject's general level of daytime sleepiness, or their average sleep propensity in daily life. It is a validated measure with high specificity and sensitivity for assessing subjective sleepiness (Johns 1991; Johns 2000; Broderick 2013), The ESS consists of 8 questions rated on a 4-point scale (0-3 corresponding to never, slight change, moderate chance, and high chance), indicating the usual chance of dozing off or falling asleep in different situations. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher the subject's average daytime sleepiness. There is a risk of pathological daytime sleepiness if the score is >10.

14.2. Brain Fog Scale

After excessive daytime sleepiness (experienced by nearly all IH patients), "brain fog" — defined as "being unable to think clearly or concentrate at any time throughout the day" (Trotti 2020) — is the second most common symptom (experienced by approximately 83% of patients) in patients with IH. "Brain Fog" or cognitive impairment is a term used for certain symptoms that can affect the ability to think and function, including a lack of mental clarity; and a feeling of being mentally sluggish and fuzzy, leading to forgetfulness, mental cloudiness, and difficulty focusing, thinking and communicating. Other symptoms include thoughts moving too quickly, detached, lost, and sleepy.

The Brain Fog scale (adapted from Ross 2013; Appendix D) consists of 3 parts as follows:

- **Part 1. Frequency:** 5 multiple choice questions about the frequency of brain fog experienced during the last week overall, on average during the day, frequency of most severe brain fog, and what activities were impaired.

- **Part 2. Severity:** Rated on a scale from 0 to 100 in 10-point intervals with higher numbers indicating increased severity.

- **Part 3. Descriptors (Symptoms):** 19 scaled questions (scale from 0 to 4) that evaluate descriptors and triggers of brain fog (corresponding to strongly agree, agree, neutral, disagree, and strongly disagree). The total score (sum of 19 items) can range from 0 to 76. The higher the Brain Fog descriptor score, the worse the

subject's brain fog.

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

The CGI-S (Guy 1976; Busner and Targum 2007, Appendix E) is a clinician-rated scale based on the response to 1 question that evaluates the severity of symptoms in the study on a scale from 1 (normal, not at all ill) to 7 (among the most severely ill patients). The Investigator will rate his/her impression of the severity of the subject's current condition relative to his/her experience with this patient population.

14.4. Patient Global Impression of Severity (PGI-S)

The PGI-S (Appendix F, adapted to IH from Viktrup 2012 and Martinez-Martin 2015) is a single-item patient-rated questionnaire of IH severity ("How would you describe your overall disease condition over the past week?"), with one of 6 possible responses: 0 (none), 1 (very mild), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe). Subjects will rate the severity of their overall IH disease condition during the past week.

14.5. IH Severity Scale (IHSS)

The IHSS (Dauvilliers 2019, Appendix G) measures severity of both nighttime and daytime IH symptoms and sleep inertia (or "sleep drunkenness") related to each, as well as impaired daytime functioning. Patients rate severity and frequency in 17 questions using a 4- or 5-point scale for each question. The total score will range from 0 to 50. A score of 22 or below is typical for people without any sleep disorder. Higher scores on the IHSS indicate more severe symptoms of IH.

14.6. Modified Karolinska Sleepiness Scale (Mod-KSS)

The Mod-KSS (Akerstedt 1990, Appendix H) is a 10-point scale used to measure at-the-moment (during first hour after awakening) sleepiness. Scores range from 1 to 10 (1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy – but no difficulty remaining awake, and 9 = extremely sleepy – fighting sleep, and an additional score for the modified version: 10 = extremely sleepy, falls asleep all the time). The modified version includes the 10-point scoring option. Scores on the Mod-KSS increase with longer periods of wakefulness. On this scale, subjects will indicate daily which level best reflects their sleepiness experienced during the first hour after awakening and in late afternoon (from 5 pm to 6 pm).

14.7. PROMIS®-29 Scales

The Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Scale, Hays 2018, Appendix I) is a NIH initiative to develop state-of-the-science self-report measures to assess functioning and well-being in physical, mental, and social domains of health (Cella 2010). Each question is rated on a scale from 1 to 5 corresponding with "Not at all", "A little bit". "Somewhat", "Quite a bit", and "Very much", or "Very Poor", "Poor", "Fair", "Good", and "Very Good", depending on the question. Domains of the system used in the study will include Fatigue, Ability to Participate in Social Roles and Activities, and Depression.

14.8. Patient-Reported Wakefulness Questionnaire (ZOGIM-A)

The ZOGIM-A scale (Shapiro 2006, Appendix J) evaluates a patient's experiences with alertness over the course of the day, querying the subjective impact of environmental factors (eg, caffeine, exercise), the anticipated benefits of increased energy levels, and the perceived proportion of the day spent at high levels of alertness. Ten items are scored using a 5-point scale ranging from 1 ("Extremely") to 5 ("Not at all"). Summing the scores obtained on each item provides a global index – lower scores denote impaired alertness while higher scores indicate high alertness.

14.9. Sleep Inertia Visual Analog Scale (SIVAS)

The SIVAS (Appendix K) is a patient-reported measure consisting of a 100-mm line with an indication at each end representing each extreme of the measure (sleep inertia in this case). Subjects will give their indication with a mark on the line corresponding to their answer. This assessment instrument has been used to measure sleep inertia at specific time points after awakening (Hayashi 2005; Takahashi and Arito 2000; Oriyama and Miyakoshi 2018). The VAS measure of sleep inertia is an at-the-moment measure of how difficult it was to awaken in the morning, with anchors at each end on the line labeled as "very easy" and "very difficult". Subjects will complete the SIVAS daily approximately 1 hour after awakening.

14.10. Sleep Diary

Subjects will keep a Sleep Diary (Appendix L) on a day-by-day basis throughout the study. The Sleep Diary is a subjective global appraisal of night and daytime sleep providing estimates of the number, duration, and chronology of daily episodes of sleep and sleepiness. The assessments collect self-reported time-in-bed, time of sleep start, night awakenings, time-out-bed, time of awakening, number of daily naps/dozes, and total daily nap duration. The Sleep Diary template used in this study and the associated instructions (Appendix L) are based on the Consensus Sleep Diary (Carney 2012). Site staff will instruct subjects how

to complete the Sleep Diary based on the instructions in Appendix L. The sleep diary should be completed within one hour after awakening in the morning, and again at night before going to sleep.

14.11. Procedure for Performing the Efficacy Assessments

- **Clinician-Reported Outcomes:** The CGI-S is a clinician-reported outcomes questionnaire. Therefore, the CGI-S will be completed by trained and qualified research site staff after evaluation of the patient.

- **Patient-Reported Outcomes:** The ESS, Brian Fog Scale, PGI-S, IHSS, Mod-KSS, PROMIS-29, ZOGIM-A, and SIVAS are patient-reported outcome questionnaires. Therefore, they will be completed by the patient, and subsequently reviewed for completeness with the patient by trained and qualified research site staff. Based on this review, appropriate corrections can be made (eg, filling in missing answers, correction of multiple answers where only 1 box should be checked). The Mod-KSS is a daily assessment with a 1-hr look back, and will be completed by the subjects at approximately 1 hour after awakening and in late afternoon (at approximately 6 pm). The SIVAS is an at-the-moment assessment that will be completed by the subjects daily at approximately 1 hour after awakening.

  In addition, daytime and nighttime sleep parameters will be derived from the Sleep Diary that subjects will complete daily. The Sleep Diary will be reviewed at each visit by study staff for completeness.

15. PHARMACOKINETIC (PK) ASSESSMENTS

15.1. Pharmacokinetic Plasma Sample Collection

Subjects will visit the study site for a PK Visit, and will stay for a minimum 1 night and day for dosing and to collect blood samples for PK over a 24-hour period, including nighttime samples. This PK Visit may coincide with Visit 6 or may occur on a separate day between Visit 5 and Visit 7.

Subjects will have PK samples collected over a 24-hour period, at the following times.

- For subjects receiving the qd pm regimen: 0 (predose), 1, 2, 4, 5, 6, 8, 10, 12, 16, and 24 hours after the pm dose.
- For subjects receiving the bid regimen: 0 (predose), 1, 2, 4, 5, 6, 8, 10, and 12 hours after the pm dose (PK Visit day), and 0 (predose), 1, 2, 4, 5, 6, 8, 10, and 12 hours after the am dose (day after PK Visit day). Since the bid regimen may be different for different subjects, with the dosing interval between the pm and am doses different

from 12 hours, the PK sampling times will need to be adjusted accordingly (see Section 1.1).

For subjects receiving the qd pm regimen, eleven (11) blood samples (4 mL each) will be collected and a total of approximately 44 mL blood per subject will be drawn for PK analysis. For subjects receiving the bid regimen, eighteen (18) blood samples (4 mL each) will be collected and a total of approximately 72 mL blood per subject will be drawn for PK analysis.

The PK samples will be collected for the measurement of the plasma concentrations of SDX, d-MPH and ritalinic acid. Detailed instructions for the collection, processing, storage and shipment of the plasma PK samples will be included in the Laboratory Manual. The date and time of collection of each PK sample will be recorded.

15.2. Pharmacokinetic Sample Shipments

The plasma samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. Prior to shipment, the samples will be appropriately packed in a Styrofoam cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 48 hours for remote shipments. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. The shipping address of the bioanalytical laboratory will be provided in the Laboratory Manual.

16. DISCONTINUATION OF SUBJECTS

16.1. Early Withdrawal of Subjects from the Study

A subject may be discontinued or choose to withdraw from study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for Early Withdrawal:

- Subject withdrawal of consent.
- Subject is not compliant with study procedures to a degree that it may affect the objectives of the study or may be a safety risk, at the discretion of the Investigator.
- Adverse event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment.
- Protocol violation requiring discontinuation of study treatment.

- Lack of efficacy (especially at the highest tolerable dose in the Titration Period).
- Lost to follow-up after a missed visit, when there is no response to two attempts by phone and a registered letter to the subject. After these 3 failed attempts, the subject will be considered lost to follow-up.
- Sponsor request for early termination of the study.
- Positive pregnancy test (tested in females of childbearing potential) before the last dose of study drug.
- Overdosage, at the discretion of the Investigator (eg, intentional overdosage, multiple occurrences of overdosage).
- Out-of-range vital signs/AEs, which are judged by the Investigator as clinically significant and that may pose a safety risk for the subject (eg, further treatment, even at a reduced dose, is not in the best interest of the subject).
- Clinically significant ECG abnormality/AEs, at the discretion of the Investigator. Abnormal ECGs will be repeated once for confirmation in which case only the repeated ECG will be recorded.
- Clinically significant suicidal ideation/behavior, based on the C-SSRS assessment at any time before the last dose of study drug.
- For other reasons (eg, Investigator/Sponsor request, inappropriate behavior, social reasons).

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed as described in Section 19.1.1.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

If a subject meets withdrawal criteria during the study the subject will be withdrawn, and Early Termination procedures will be completed.

16.2. Replacement of Subjects

Screening and enrollment of new subjects will continue until at least 48 subjects are randomized in the Withdrawal Period. The required number of subjects may be increased based on the interim analysis.

17. STUDY ENDPOINTS

The following endpoints will be used:

17.1. Safety Endpoints

The Primary Endpoint is the safety and tolerability based on the following assessments: The occurrence of Treatment-Emergent Adverse Events (TEAEs), physical examinations, clinical laboratory tests (chemistry, hematology, and urinalysis), ECGs, vital signs, body weight, C-SSRS, and PSQI-Q6.

The occurrence of AEs will be assessed following enrollment (signing of consent) and ending with the Follow-Up Phone Call or Early Termination. AEs will be classified as TEAEs when they occurred after administration of the first dose of study drug.

17.2. Efficacy Endpoints

Secondary Endpoints (Efficacy) will be assessed as the change from baseline of the following assessment scores during the Double-Blind Withdrawal Period (Visit 7 to Visit 8):

- Excessive Daytime Sleepiness (EDS) assessed with the Epworth Sleepiness Scale (ESS) (Johns 1991, Appendix C).
- "Brain Fog" (Brain Fog Scale) (Ross 2013, Appendix D).
- Clinical Global Impression of Severity (CGI-S) score (Guy 1976; Busner and Targum 2007, Appendix E).
- Patient Global Impression of Severity (PGI-S) score (Viktrup 2012; Martinez-Martin 2015; Appendix F).
- IH Severity Scale (IHSS) Total Score (median) (Dauvilliers 2019, Appendix G).
- Morning sleepiness (Mod-KSS score) (Akerstedt 1990, Appendix H), collected daily starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit.
- Selected domains of PROMIS®-29: (Hays 2018, Appendix I).
    - Fatigue
    - Social Functioning (Ability to participate in Social Roles and Activities)
    - Depression
- Patient-reported wakefulness (ZOGIM-A score) (Shapiro 2006, Appendix J).
- Sleep Inertia Visual Analog Scale (SIVAS) (Appendix K), collected daily starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit.
- Data collected or calculated from the Sleep Diary (Appendix L): Collected daily starting from 10 days prior to Visit 2 to Visit 8 or the Early Termination Visit. The

most important nighttime sleep-related parameter is Total Sleep Time (TST); the most important daytime sleep-related parameter is Total Nap Time (TNT). The method of reporting TST from a sleep diary has been used in clinical practice and research in IH (Dauvilliers and Buquet 2005; Lawrence 2018, Mallinson 2019), as it provides a measure of sleep in the home environment over a longer period of time than what is feasible during study visits or in a sleep laboratory.

The primary efficacy endpoint is the change in ESS from Visit 7 to Visit 8.

All retrospective efficacy endpoints (all efficacy endpoints except at-the-moment SIVAS and Mod-KSS) will be assessed with a look-back period of 1 week.

All efficacy endpoints will also be analyzed during the visits of the Open-Label Titration Period (Visit 2 to each of Visits 3-7).

17.3. Pharmacokinetic Endpoints

The following key steady-state PK parameters will be calculated for SDX, d-MPH, and ritalinic acid, in subjects with adequate PK data: $AUC_{0\text{-}24h,ss}$, $C_{max,ss}$, $T_{max,ss}$, and $C_{min,ss}$. The primary PK endpoint is the $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ of d-MPH.

For the bid regimen, applicable PK parameters will be calculated separately for the pm and am doses.

18. STATISTICS

Details of the statistical analyses will be defined in the Statistical Analysis Plan (SAP). Prior to database lock, a detailed SAP will be written describing all analyses that will be performed.

18.1. Sample Size Calculation

Since this is an exploratory study to determine the effect size, dose range and best dosing regimen of SDX for the treatment of IH, no formal sample size calculations were performed. However, the chosen sample size would be powered at 80% to detect an effect size of 1.2; a study of a wake-promoting agent in narcolepsy achieved an effect size of approximately 1.0 on the ESS (Watson 2021). A second study of a CNS sedating agent (Sodium oxybate) in IH achieved an effect size of 1.6 on the ESS (Dauvilliers 2021). In both cases, the standard deviation of the difference between active and placebo for ESS was approximately 4.0. This standard deviation would yield a confidence interval of ±3.2 around the two placebo/active comparisons in this study.

A non-binding interim analysis following the exit from the study of the first 50% of

randomized subjects will evaluate the conditional power and potentially increase the sample size (see Section 18.3.5).

18.2. Populations for Analysis

- **Titration Safety Population:** All enrolled subjects who received at least one dose of study drug and who have at least one post-dose safety assessment. Safety measures will be analyzed for all subjects in the Titration Period by dosing regimen. Demographics and baseline characteristics will be summarized for this population when describing all subjects treated.

- **Withdrawal Safety Population:** All subjects randomized to a treatment in the Double-Blind Withdrawal Period who received at least one dose of study drug in that period and who have at least one post-dose safety assessment in the Double-Blind Withdrawal Period. Safety measures will be analyzed for subjects in the Withdrawal Period by treatment and regimen (and pooled across regimen). Demographics and baseline characteristics will be summarized for this population when describing subjects entered into the Withdrawal Period.

- **PK Population:** All subjects who provided adequate PK samples to calculate the steady-state plasma exposure of d-MPH and who do not have major protocol deviations that could potentially affect the PK conclusions of the study. Data from the PK Population will be used for PK data listings and PK analyses.

Efficacy analyses will be conducted in the following populations:

- **Titration Modified Intent-to-Treat (MITT) Population:** All randomized subjects in the Titration Period who received at least one dose of study medication and have at least one post-randomization ESS score in the Titration Period. Demographics and titration baseline characteristics will be summarized for the Titration MITT Population.

- **Withdrawal MITT Population**: All subjects in the Withdrawal Period who received at least one dose of study medication and have at least one post-randomization ESS score in the Withdrawal Period. Demographics and randomization baseline characteristics will be summarized for the Withdrawal MITT Population.

18.3. Statistical Analyses

18.3.1. Safety Analysis

Safety analyses will be reported separately for the Titration Period and the Double-Blind Withdrawal Period using the respective safety populations for each. Reporting will be by regimen in the titration period and by treatment and regimen in the double-blind period.

Safety analyses will be performed by descriptive statistics, without formal statistical testing (except for PSQI-Q6). Subgroup analyses for safety will be performed by gender.

PSQI-Q6 scores will be analyzed similarly to the continuous efficacy endpoints.

Clinical laboratory, vital signs, body weight, and ECG parameters will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by regimen and visit for the Titration Period and by treatment and visit for the Double-Blind Withdrawal Period. Those subjects with significant laboratory abnormalities will be identified in data listings.

AEs will be mapped to system organ classes and preferred terms using a recent version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs with new onset during the study after the first dose of study drug until the Follow-Up Visit or Early Termination Visit will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

TEAEs will be summarized by system organ class and preferred term, and by regimen and visit for the Titration Period and by treatment and visit for the Double-Blind Withdrawal Period. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates by severity. A summary of SAEs, and AEs leading to early discontinuation from the study will be presented.

In summarizing the subject incidence of AEs, multiple events with the same preferred term or with increases in severity will only be counted as 1 AE and summarized at the maximum severity. Subject incidence is similarly defined for multiple events within the same system organ class. Summaries by period will be based on AEs considered emergent within each period.

AEs of Special Interest (AESIs, Section 19.3) will be summarized and analyzed separately from other AEs (and separately for Abuse-Related AEs and Cardiovascular AEs).

For the titration period, the safety analyses will include the number and percentage of subjects successfully titrated, titrated dose, AE profile, and reasons for withdrawal in the

titration period.

Details of the safety analyses will be provided in the SAP.

18.3.2. Efficacy Analysis

18.3.2.1. Descriptive Statistics and General Reporting

Changes from titration and randomization baseline of all efficacy assessments at each subsequent visit will be summarized descriptively. Categorical responses to efficacy questionnaires will be summarized by the number and percentage of subjects who selected each response.

Comparisons between treatments will be conducted for each dosing regimen. Other comparisons may include an analysis with data pooled from both dosing regimens and a direct comparison of both dosing regimens.

All statistical tests will be for information purposes only.

18.3.2.2. Primary Estimand

Study population: The population will be subjects with IH as defined by the inclusion/exclusion (see Section 7.2) that are successfully titrated, meet the criteria for the Randomized Withdrawal Period (see Section 8.3), and received at least one dose of study medication and have at least one post-randomization ESS score in the Withdrawal Period (Withdrawal MITT Population).

Endpoint: The change in a subject's ESS score in the Withdrawal MITT Population at the end of the Withdrawal Period (Visit 8) compared to the randomization baseline at the start of the Withdrawal Period (Visit 7).

Analysis: The primary efficacy evaluation will be based on the difference (SDX minus placebo) for each regimen in least squares mean estimates of the change from baseline score, obtained from an ANCOVA that includes randomization baseline ESS, treatment (active or placebo), regimen (bid or qd), and treatment by regimen as covariates.

Intercurrent Events: A while-on-treatment strategy will be utilized; because the period from the baseline to end of Withdrawal Period is quite short, it is anticipated that there will be very few discontinuations. Additionally, the visit window of up to ±3 days for Visit 8 allows some flexibility to maximize the number of subjects completing the two week Withdrawal Period. Subjects who do not complete Visit 8 will not have a post-

randomization ESS score and will be excluded from the Withdrawal MITT Population. Other intercurrent events such as use of prohibited medications will not have any special handling.

Continuous additional efficacy endpoints, if appropriate, will be analyzed with the same analysis method as the main analysis.

18.3.2.3. Secondary and Other Efficacy Analyses

For the analyses in the Titration Period, the titration baseline (Visit 2) will be used for calculating the change from baseline and the Titration MITT Population will be utilized. Differences in the regimens at each time point collected will be reported.

Analysis of the change in CGI-S and PGI-S responders from baseline to each post-baseline visit will be evaluated at each post-baseline visit within each treatment group using the Pearson chi-square test (equivalent to the difference in proportions z-test).

Subgroup analyses for efficacy will be performed by gender, in subjects with and without long sleep times, in subjects with and without sleep inertia, and in subjects with and without brain fog. A long sleep time is defined as a TST >10 hours based on the Sleep Diary during the last 10 days prior to Visit 2 (using the last 7 days with complete Sleep Diary data, or less if not available). Subjects with sleep inertia will be identified based on the titration baseline IHSS (Visit 2). Subjects with Brain Fog will be identified based on the titration baseline Brain Fog Scale (Visit 2).

Details of the efficacy analyses will be provided in the SAP.

Sleep Parameters

The following sleep parameters will be extracted or calculated (Reed and Sacco 2016) from the Sleep Diary (Appendix L):

Parameter	Description
TIB	Time in Bed: Time from going to bed until getting out of bed.
DSE	Duration of Sleep Episode: Time from trying to sleep to time of final awakening. The relationship between the sleep parameters during this period: DSE = SOL + TST + WASO + TASAWA
SOL	Sleep Onset Latency: The amount of time from "lights out," or bedtime for nighttime sleep, to actually falling asleep.
WASO	Time Awake after Sleep Onset before final awakening: total duration of awakenings during a planned sleep episode (nighttime sleep).
TASAFA	Time Attempting to Sleep After the Final Awakening: Time between final awaking from nighttime sleep and getting out of bed after nighttime sleep.
TST	Total Sleep Time: The amount of time that a person spends actually sleeping during a planned sleep episode (nighttime sleep), calculated as TST = DSE – (SOL + WASO + TASAWA).
SEF [a]	Sleep efficiency: The proportion of time during a sleep episode that is actually spent sleeping. SEF is calculated by dividing total sleep time by total time in bed. SE is calculated as follows: SEF = TST / DSE x 100
NN	Number of naps or dozes[b] during the day (after awakening from nighttime sleep and before going to bed for nighttime sleep)
TNT	Total Nap Time: total duration of naps or dozes during the day (after awakening from nighttime sleep and before going to bed for nighttime sleep)

a. Commonly abbreviated as SE but abbreviated as SEF for this study to avoid confusion with SE for Standard Error.
b. Nap: A short sleep period, usually taken intentionally during the day, apart from a person's primary (nocturnal) sleep period; Doze: A brief period of unintentionally falling asleep.

The most important nighttime sleep-related parameter is TST; the most important daytime sleep-related parameter is TNT.

Details of the calculations and statistical analyses of the sleep parameters will be listed in the SAP.

18.3.3. Baseline for Safety and Efficacy Analyses

- The baseline for the safety analyses is Visit 2 before administration of the first dose of study drug.
- The baseline for the efficacy analyses in the Titration Period is the titration baseline (Visit 2) before administration of the first dose of open-label study drug.
- The baseline for the efficacy analyses in the Withdrawal Period is the randomization baseline (Visit 7) before administration of the first dose of double-blind study drug.

The key baseline characteristics will be summarized descriptively per treatment arm.

Details of the analyses of the baselines for safety and efficacy will be provided in the SAP.

18.3.4. Study Drug Exposure and Compliance

The number of dosing units dispensed and returned will be accounted for by site staff. Exposure and compliance will be calculated based on the number of dosing units dispensed and returned. Acceptable compliance is defined as 80-100% (inclusive).

The number and percentage of subjects compliant with study treatment will be tabulated. The total number of doses taken as well as the mean, standard deviation, minimum, median and maximum number of doses received will be tabulated overall and by visit, beginning with Visit 3, the first visit in which study drug is returned, till Visit 8, the last visit in which study drug is returned.

The mean daily dose of SDX (mg) and the mean daily dose of SDX by body weight (mg/kg) will be calculated by visit, and will be compared over time to show dose changes over the course of the study. This will consider changes in dose since the Investigator may increase or decrease the dose of SDX during the Titration Period, based on individual tolerability and effect.

The number and percentage of subjects for each dose level will be calculated based on the optimized dose.

All study drug exposure and compliance analyses will be done separately for the Titration Period and the Withdrawal Period, and overall, and by treatment.

Details of the analyses of drug exposure and compliance will be provided in the SAP.

18.3.5. Interim Analysis

An interim analysis based on the change from the end of the Open-Label Titration Period to the end of the Double-Blind Withdrawal Period in ESS is planned once the first 50% (24 subjects) of the initially planned sample size have completed or discontinued from the Double-Blind study period. This will be completed independently within each regimen using conditional power to determine whether an increase in sample size is recommended for that regimen. The conditional power will be calculated within regimen based on the first cohort, using the following formula (Mehta and Pocock 2010):

$$CP(Z_1, \check{n}_2) = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\check{n}_2}} - \frac{z_1\sqrt{\check{n}_2}}{\sqrt{n_1}}\right)$$

where:

Z_1 = the value of the Z score for each regimen at the interim for the contrast described above (this will use the inverse normal to convert the p-value from the t statistic to the equivalent Z)
n_1 = the actual sample size for each regimen at the interim
n_2 = the total planned sample size for each regimen (24 patients)
$\check{n}_2$ = the total planned sample size minus the actual sample size at the interim

An unblinded team, isolated from all study operations, will perform the analysis and return a recommended sample size increase; any increase will be capped at 12 additional subjects in each regimen (4 placebo and 8 active in each of the qd pm and bid dosing regimens). Other than the recommendation, the Sponsor will remain blinded to the interim results as well as individual subject assignments.

To account for the blinded interim sample size re-estimation, data from the interim and post-interim cohorts will be combined within regimen using the inverse normal method using the Cui, Hung, Wang (CHW) approach (Cui 1999):

$$Z_1 = \Phi^{-1}(1 - p_1)$$

$$\text{and} \quad Z_2 = w_1 Z_1 + w_2 \Phi^{-1}(1 - p_2) \tag{1}$$

where:
Z_1 = the Z statistic for the first stage
Z_2 = the combination test statistic at the end of the second stage
w_i = the weighting applied for each associated Z statistic
p_1 = the first stage p-value based on the t-statistic for primary efficacy endpoint
p_2 = the second stage p-value based on the t-statistic for second stage subjects for primary efficacy endpoint

The weights are defined prospectively according to the square-root of the planned proportion of subjects in the 2 stages, relative to the pre-planned total enrollment of 24 subjects (in each regimen), as $w_i = \sqrt{0.5}$. To control the type I error, adaptive changes of the stage wise sample sizes will not lead to changes of the weights (Lehmacher and Wassmer 1999).

For each difference of interest, the point estimate of the difference and adjusted 95% CI will be provided (Lawrence and Hung 2003). The point estimate of the active versus placebo treatment difference is provided in equation (2) and its adjusted CI is provided in equation (3).

$$\hat{\delta} = \frac{r_1 \hat{\delta}^{(1)} + \sqrt{1 - r_1}\sqrt{N^* - r_1}\,\hat{\delta}^{(2)}}{r_1 + \sqrt{1 - r_1}\sqrt{N^* - r_1}} \tag{2}$$

$$\hat{\delta} \pm \left(\left| \frac{\hat{\delta}}{Z_2} \right| z_{\alpha/2} \right) \quad (3)$$

where:
$\delta^{(1)}$ = the LS mean difference from stage 1 analysis (interim cohort analysis)
$\delta^{(2)}$ = the LS mean difference from stage 2 analysis (post-interim cohort analysis)
r_1 = the total number of patients planned to be included at the interim analysis divided by the total number of patients originally planned (planned sample size), ie, 0.5
N^* = the final total number of patients divided by the total number of patients originally planned
Z_2 = the combination test statistic at the end of the second stage obtained in equation (1)

Full details will be provided in an Interim Analysis Charter and the Statistical Analysis Plan.

18.3.6. Subgroup Analyses

Subgroup analyses will include safety, efficacy, and PK endpoints by gender. In addition, subgroup analyses for efficacy will be conducted in subjects with and without long sleep times, in subjects with and without sleep inertia, and in subjects with and without brain fog. Subgroup analyses will be performed for the Titration Period and for SDX vs placebo in the Withdrawal Period.

Details of the subgroup analyses will be provided in the SAP.

18.3.7. Tabulation of Individual Participant Data

A listing of date and type of each subject's TEAEs will be provided.

18.3.8. Pharmacokinetic Analysis

PK parameters will be calculated from plasma concentrations of SDX, d-MPH, and ritalinic acid using standard, non-compartmental methods in a recent version of Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ).

Concentrations that are below the limit of quantification (BLQ) will be treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations will be treated as zero from time zero up to the time at which the first quantifiable concentration is observed; embedded and/or terminal BLQ concentrations will be treated as "missing".

The following pharmacokinetic parameters will be calculated:

Parameter	Description
$AUC_{0\text{-}24h,ss}$	The area under the plasma concentration versus time curve from time zero to 24 hours post-dosing at steady state (based on a 24-hour dosing interval for all dosing regimens)
$AUC_{am,ss}$	The steady state AUC after the morning dose (bid regimen only), using the actual am dosing interval
$AUC_{pm,ss}$	The steady state AUC after the evening dose (bid regimen only), using the actual am dosing interval
$AUC_{0\text{-}12h,ss}$ [a]	The steady state AUC after the morning dose (bid regimen only), extrapolated or interpolated to 12 hours postdose (12-hour dosing interval)
$AUC_{12\text{-}24h,ss}$ [a]	The steady state AUC after the evening dose (bid regimen only), extrapolated or interpolated to 12 hours postdose (12-hour dosing interval)
$C_{max,ss}$	The maximum plasma concentration at steady state. For the bid regimen, separately for the pm and am doses.
$T_{max,ss}$	The time of occurrence of C_{max} at steady state. For the bid regimen, separately for the pm and am doses.
$C_{min,ss}$	The trough concentration at steady state. For the bid regimen, separately for the pm and am doses.
FLUCP	Percent peak-to-trough fluctuation. For the bid regimen, separately for the pm and am doses.
CL_{ss}/F	The apparent total plasma clearance at steady state after daily oral dosing (L/h), based on a 24-hour dosing interval for all dosing regimens.
$CL_{ss}/F/W$	CL_{ss}/F normalized by body weight (W), in L/h/kg.

a. Since the dosing interval of the bid regimen will be different for different subjects (since it is defined by the subject's time of awakening and the time going to bed), the am dosing interval could be longer than 12 hours and the pm dosing interval could be shorter than 12 hours. Therefore, AUC values will be adjusted (interpolated or extrapolated) to obtain $AUC_{0\text{-}12h,ss}$ for descriptive statistics and am-pm comparisons.

For each treatment, the dose of SDX will be used for the calculation of CL/F of SDX. For the calculation of CL/F of d-MPH and ritalinic acid after administration of SDX, the molar equivalent d-MPH and ritalinic acid amount of the SDX dose will be used.

Descriptive Statistic and Plots

For each PK parameter and for each analyte per treatment (dose and dose regimen), descriptive statistics will be calculated.

Individual plasma concentrations and PK parameters and descriptive statistics by dose and dose regimen will be listed. Individual subject and mean plasma concentration-time profiles will be plotted for all analytes by dose and dosing regimen on linear and logarithmic

concentration axes.

Statistical PK Comparison between Treatments
The PK exposure parameters ($C_{max,ss}$, $AUC_{0-24h,ss}$) of d-MPH will be compared between treatments (dose and dosing regimen) using the appropriate statistical test. Comparisons of the PK exposure parameters will also be performed based on pooled values for all doses (within a dose regimen group) after dose-normalization of the parameters.

Key PK parameters ($C_{max,ss}$, $T_{max,ss}$, $AUC_{0-12h,ss}$) of d-MPH will also be compared between the morning and evening dose administrations (bid regimen only), to test whether there are diurnal differences in exposure or time to maximum exposure.

The same statistical assessments will be performed for SDX.

Details of the PK analyses will be provided in the SAP.

18.3.9. Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

The PK/PD analysis will consist of an evaluation of the relationship between changes from baseline of the efficacy endpoints and the systemic exposure of d-MPH, with tabulations and graphical methods, including comparisons between treatments. Methods may include regression analyses between efficacy variables and d-MPH PK variables (for example, efficacy variable vs $C_{max,ss}$ and $AUC_{0-24h,ss}$ of d-MPH). The main efficacy variable will be the ESS score, but other efficacy variables may be analyzed as well.

Details of the PK/PD analyses will be provided in the SAP.

19. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

19.1. Adverse Events (AEs)

19.1.1. Recording, Monitoring and Follow-Up of AEs

Adverse Events (including SAEs) will be recorded and monitored for all subjects from the moment they are screened (at the time of signing written consent) until they complete the study at the EOS (the Follow-Up Phone Call or the Early Termination Visit). The onset date for these AEs will fall within the period of enrollment to EOS.

Follow-up of AEs and SAEs will be performed according to the following criteria:

- All AEs and SAEs will be followed from enrollment to EOS until the abnormal parameter or symptom has resolved or stabilized.

- Only AEs and SAEs assessed as related to study drug will be followed for as long as necessary (past EOS, if necessary) to adequately evaluate the subject's safety, ie, until resolution or until the event stabilizes, or until the subject is lost to follow-up. For AE and SAEs required to be followed past the EOS, the outcome at the time of the final study visit (EOS visit) will be recorded. In addition, for SAEs, follow-up information will be reported.

The Investigator or Sub-Investigator is responsible for ensuring that follow-up includes any supplemental investigations to elucidate the nature and causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

19.1.2. Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. AEs include, but are not limited to:

1. Clinically significant adverse changes (as assessed by the Investigator or designee) from baseline clinical status in ECGs, routine laboratory tests, and physical examinations
2. A worsening or change in nature, severity, or frequency of conditions present at the start of the study
3. Subject deterioration due to primary illness. Symptoms of the underlying medical condition of IH (eg, excessive sleepiness, prolonged nighttime sleep, or sleep inertia) are not considered AEs unless there is a worsening of the subject's IH symptoms in comparison to symptoms that the subject experienced before the initiation of treatment in the study.
4. Intercurrent illness
5. Drug interaction

All AEs, whether observed by the Investigator or Sub-Investigator, reported by the subject, determined from laboratory findings, or other assessments, will be documented. Adverse events will be recorded in the patient eCRF Adverse events will be described by duration (start and stop dates and times), seriousness, severity, causal relationship to study drug (or if unrelated, the cause, if known), treatment (and other actions taken) and outcome, including whether or not it caused the subject to discontinue from the study.

The Investigator or Sub-Investigator will initially question the subject in a general way, without asking about the occurrence of any specific symptom. However, if the subject reports any AE, the Investigator or designee Sub-Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE. The AE term should be reported in standard medical terminology, if possible.

An unexpected AE is one of a type not identified in nature, severity, or frequency in the current KP1077 Investigator's Brochure or of greater severity or frequency than expected based on the information in the KP1077 Investigator's Brochure.

19.1.3. Severity

Adverse Events shall be graded with regard to severity according to criteria defined in the Common Terminology Criteria for Adverse Events v6.0 (CTCAE) by the Investigator or Sub-Investigator. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

19.1.4. Causal Relationship to Study Drug

The causal relationship of an AE to the study drug should be assessed using the following criteria:

Classification	Criteria
Related or Suspected to be Related to Study Drug	***There is a reasonable possibility that the study drug caused the event - ie, there is evidence to suggest a causal relationship between the study drug or procedure and the AE.*** Some temporal relationship exists between the event and the administration of the study drug or procedure, and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident. The event follows a reasonable temporal sequence from administration of the study drug or procedure and at least 1 of the following instances of clinical evidence: • The event follows a known or suspected response pattern to the study drug or procedure. • The event improves upon stopping the study drug or procedure or decreasing the dose. • The event reappears upon repeated exposure, if medically appropriate.
Not Related to Study Drug	***There is not a reasonable possibility or clinical evidence that the study drug caused the event.*** The event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.

19.2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Is fatal (results in death)
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Note that AEs of Grade 3 due to hospitalization or prolongation of a hospitalization, and Grade 4 and Grade 5 per CTCAE grading criteria are classified as SAEs.

The following hospitalizations do not require classification and reporting as an SEA:

- Planned hospitalization prior to subject's enrollment in the study
- Hospitalization for social reasons and respite care, in the absence of any deterioration in the subject's general condition
- Hospitalization elective in nature and not related to worsening of an underlying condition

Complications that occur during any hospitalization, and complications that prolong any hospitalization, are SAEs.

Overdose, medication errors, and drug misuse of the study drug are SAEs only if any of the seriousness criteria are met.

19.2.1. Serious Adverse Event Reporting

Within 24 hours after a SAE detection, observation, or report of occurrence (regardless of the relationship to test article), the Investigator or designee will enter the SAE into the electronic database. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the appropriate sponsor contact. If the EDC system is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to the appropriate sponsor contact. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

If EDC is not functional, a paper SAE form will be utilized and provided to the following contact:

Rho, Inc
2635 E NC Hwy 54
Durham, NC 27713
SAE Help Line: 888-754-7231
SAE Fax Line: 888-746-3293
Email: rho_productsafety@rhoworld.com

These SAE reports must contain the following information:

1. Study name/number
2. Study Drug
3. Investigator details (name, phone, fax, e-mail)
4. Subject Number
5. Subject Demographics (age, sex, body weight)
6. Clinical Event
7. Description
    a. Diagnosis
    b. Date of onset
    c. Treatment (drug, dose, dosage form)
    d. Concomitant medications
    e. AE Relationship to study drug
    f. Action taken regarding study drug in direct relationship to the AE
    g. Criteria for "Serious" applicable to the AE
8. Cause of death (whether or not the death was related to study drug)
9. Autopsy findings (if available)

Any SAE that occurs during the study should be recorded by each clinical site, and reported to the CRO. The CRO will notify the Sponsor by the end of the next business day after SAE notification receipt from the site.

SAEs considered "Related or Suspected to be Related to Study Drug" shall also be classified as being "expected" or "unexpected." An unexpected event is one that is not listed in the KP1077 Investigator's Brochure.

The person responsible for the study shall ensure the study has been carried out in accordance with local pharmacovigilance regulations.

All serious event reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts) and 21 CFR 314.80 for marketed drugs (15-day alerts). Unexpected fatal or life-threatening SAEs considered related to the study drug should be reported to the FDA by Sponsor with an IND Safety report within 7 days. The Institutional Review Board (IRB)

will be notified of the alert reports per FDA regulations.

19.3. Adverse Events of Special Interest (AESIs)

AEs associated with abuse potential (FDA 2017) and cardiovascular AEs will be documented and analyzed separately from other AEs, and case narratives will be provided in the CSR. Abuse-related AEs and cardiovascular AEs will be flagged in the individual subject listings to show the incident that led to the AEs, the time at which AEs appeared following drug administration, the duration of the AEs, and which AEs overlapped temporally.

19.3.1. Adverse Events Related to Abuse Potential

In accordance with the 2017 FDA Guidance for Industry, Assessment of Abuse Potential of Drugs,(FDA 2017, Sellers and Romach 2018), abuse-related AEs will be analyzed in the Titration Period and in the Withdrawal Period using the following MedDRA preferred terms:

- Euphoria-related terms: Euphoric mood; elevated mood, feeling abnormal; feeling drunk; feeling of relaxation; dizziness; thinking abnormal; hallucination; inappropriate affect; hypnagogic hallucination, hypervigilance.
- Terms of altered attention, cognition and mood: Somnolence; affective disorders; mood disorders and disturbances, change in sustained attention, disturbance in attention, irritability, mood altered, mood swings, restlessness.
- Dissociative/psychotic terms: psychosis; psychotic disorder; aggression; confusional state, and disorientation.
- Related terms not captured elsewhere: drug tolerance; habituation; drug withdrawal syndrome; substance use disorder; substance-related disorders.
- Other abuse-related terms: depressed mood; feeling jittery; energy increased; emotional disorder; logorrhea; agitation, balance disorder, anxiety, muscle contractions involuntary, sensory level abnormal.

19.3.2. Cardiovascular Adverse Events

Because CNS stimulants including d-MPH, are sympathomimetic agents that increase noradrenergic and dopaminergic transmission, there is a known potential for adverse impacts on cardiac functioning with these medications. Therefore, cardiovascular AEs will be analyzed as AESIs. Cardiovascular AEs previously observed after treatment with SDX include: sinus tachycardia, palpitations, heart rate increase, ECG ST segment depression, and blood pressure increase.

19.4. Adverse Event Treatment and Follow-Up

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the electronic Case Report Form (eCRF). Treatment may be rendered on site under the direction of the Investigator as appropriate. Events requiring diagnostic evaluation or treatment beyond the scope of what is available and appropriate within the clinical research unit shall be referred in a timely basis to other care providers. Records of diagnostic and therapeutic interventions shall be requested in compliance with HIPAA requirements, and those received shall be retained in the subject's file.

For SAEs that occur during the study, the assessment, treatment, and follow up shall be performed for up to at least 30 days after last dose for events considered "Related or Suspected to be Related to Study Drug", and continued until resolved or clinically stable.

19.5. Overdosage

For the purposes of this clinical trial, overdosage is defined as the administration of a supratherapeutic dose, a daily dose of study drug larger than the highest dose used in the study, ie, >320 mg/day SDX. Notifications of known incidences of subjects taking more than 320 mg/day of study drug will be provided by each study site to the CRO. The CRO will notify the Sponsor within 48 hours after CRO's notification receipt from the site.

Notifications of known incidences of subjects taking more than the daily dose of study drug determined for their treatment by, the Investigator will be recorded.

If there is an associated AE or SAE associated with overdosages (>320 mg/day SDX) or with subjects taking more than the daily dose determined by the Investigator, the site is to report the event on the electronic case report form within 24 hours.

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis (Azstarys US Prescribing Information 2021).

20. PREGNANCY

Females with a positive pregnancy test will terminate the study early. The initial report of a

pregnancy during the study will be provided by the site to the CRO. The CRO will notify the Sponsor before the end of the next business day after CRO's notification by the site. The study site will report the pregnancy to the IRB within a period after the incident identification as required by the IRB.

All pregnancies will be followed to at least the completion/termination of the pregnancy. The Investigator or designee will document the subject visits accordingly and record the information in the clinical site's source documents. If the pregnancy continues to delivery, the outcome (health of the infant), in addition to the maternal health status, must be included in the report. If the subject declines the follow-ups, this will be documented in the source documents. If the subject is lost to follow-up, this will be documented in the source documents. The subject will be considered lost to follow-up when there is no response to at least two attempts to contact the subject by phone and a registered letter to the subject (after these 3 failed attempts).

Pregnancy will not be considered an AE or SAE; any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

21. PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare. Examples of protocol violations may include the following:

1. Inadequate or delinquent Informed Consent
2. Inclusion/exclusion criteria not met
3. Unreported Serious Adverse Events
4. Improper breaking of the blind
5. Multiple visits missed or outside permissible windows (at the discretion of the Investigator)
6. Materially inadequate record keeping
7. Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
8. Repeated (at the discretion of the Investigator) non-compliance with study requirements

It is the Site Investigator's responsibility to report to the IRB any Protocol Violation(s) according to the IRB's policy. A copy of the IRB submission will be filed in the site's regulatory binder and in the Sponsor's files at the CRO.

22. DATA MANAGEMENT AND RECORD KEEPING

22.1. Data Management

Data will be recorded at the site on eCRFs. All entries on an eCRF are ultimately the responsibility of the Site Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All source documentation forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed and dated. An eCRF must be completed for each participant who has provided written consent. The eCRFs and source documents must be made available to the Sponsor and/or its representatives at each site visit and/or remotely, if necessary due to on-site restriction.

22.2. Record Keeping

The Site Investigators and Contract Research Organization (CRO) must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to, protocol, eCRFs, AE reports, subject source data (including records of subjects, subject visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, and monitor visit logs.

The Site Investigators, their affiliated Institutions and the CRO should maintain the trial documents as required by the applicable regulations, and should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's and CRO's archives until written authorization is obtained from the Sponsor.

22.3. Access to Source Data/Documents

The Site Investigators and CRO agree that the Sponsor, their representatives, the IRB, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

23. QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor and/or Sponsor's representatives will perform quality control and quality assurance checks of this clinical trial that it sponsors. Before the enrollment of any patient in this study, personnel of the CRO will review with the Site Investigators and site personnel the appropriate documents and processes to conduct the trial including the protocol,

Investigator's Brochure, eCRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by CRAs from the CRO, or—as needed--other CRO personnel and/or other Sponsor personnel and/or representatives. During these visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, CRO personnel will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to Site Investigators.

The CRO and Sponsor agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol and with the United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and all applicable local ethical and legal requirements.

24. ETHICS AND REGULATORY CONDUCT OF THE STUDY

This clinical trial will be conducted in compliance with the protocol and with the United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and all applicable local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study, the 2013 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association:
https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

25. INSURANCE

25.1. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Site Investigators and the other collaborators from maintaining their own liability insurance policy. An insurance

certificate will be provided to the IRB according to regulatory requirements.

26. COMPLETION OF STUDY

The end of the study will be at the time of the last subject, last visit. The IRB will be notified about the end of the study according to regulatory requirements.

27. STUDY ADMINISTRATIVE INFORMATION

27.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the Site Investigators by the CRO. All substantial protocol amendments will undergo the same review and approval process as the original protocol and may be implemented after it has been approved by the IRB unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB according to all relevant regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of subjects in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any Investigational Medicinal Product used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB and will be communicated to the Site Investigators by the CRO.

28. REFERENCES

Acquavella J, Mehra R, Bron M, Suomi J, Hess G. Prevalence of narcolepsy and other sleep disorders and frequency of diagnostic tests from 2013-2016 in insured patients actively seeking care. J Clin Sleep Med. 2020 Aug;16(8):1255-1263.

Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci. 1990;52(1-2):29-37.

Akerstedt T, Anund A, Axelsson J, Kecklund G. Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. J Sleep Res. 2014;23(3):240-252.

Akimoto H, Honda Y, Takahashi Y. Pharmacotherapy in narcolepsy. Dis Nerv Syst. 1960 Dec;21:704-706.

Ali M, Auger RR, Slocumb NL, Morgenthaler TI. Idiopathic hypersomnia: clinical features and response to treatment. J Clin Sleep Med. 2009;5(6):562-568.

American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders, 3rd ed (ICSD-3). Darien, IL: 2014

Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep. 2007;30(10):1274-1281.

Arvidsson M, Franck J, Ackehed G, Pettersson BM, Ekström L, Rosenborg S, Dahl ML. Plasma concentrations of methylphenidate enantiomers in adults with ADHD and substance use disorder, with focus on high doses and relationship to carboxylesterase activity. Basic Clin Pharmacol Toxicol. 2022;130:491-500.

Azstarys Prescription Information. Corium, Inc, Grand Rapids, MI, 2021.

Billiard M. Idiopathic hypersomnia. Neurol Clin. 1996;14(3):573-582.

Billiard M, Dauvilliers Y. Idiopathic Hypersomnia. Sleep Med Rev. 2001;5(5):349-358.

Billiard M, Sonka K. Idiopathic hypersomnia. Sleep Med Rev. 2016;29:23-33.

Broderick JE, Junghaenel DU, Schneider S, Pilosi JJ, Stone AA. Pittsburgh and Epworth sleep scale items: accuracy of ratings across different reporting periods. Behav Sleep Med. 2013;11(3):173-188.

Bruck D, Parkes JD. A comparison of idiopathic hypersomnia and narcolepsy-cataplexy using self report measures and sleep diary data. J Neurol Neurosurg Psychiatry. 1996;60(5):576-578.

Busner J, Targum SD. The Clinical Global Impressions Scale: Applying a research tool in clinical practice. Psychiatry 2007;4:28–37.

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research 1989;28(2):193-213.

Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM.

The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.

Cella D, Riley W, Stone A, et al. Initial Adult Health Item Banks and First Wave Testing of the Patient-Reported Outcomes Measurement Information System (PROMIS™) Network: 2005–2008. Journal of clinical epidemiology. 2010;63(11):1179-1194.

Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999; 55(3):853-857.

Daly DD, Yoss RE: The treatment of narcolepsy with methyl phenylpiperidylacetate: A preliminary report. Proc Staff Meet Mayo Clin 1956;31:620-625.

Dauvilliers Y, Buguet A. Hypersomnia. Dialogues Clin Neurosci. 2005;7(4):347-356.

Dauvilliers Y, Roth T, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate, modafinil, and their combination on disrupted nighttime sleep in narcolepsy. Sleep Med. 2017;40:53-57.

Dauvilliers Y, Evangelista E, Barateau L, Lopez R, Chenini S, Delbos C, Beziat S, Jaussent I. Measurement of symptoms in idiopathic hypersomnia: The Idiopathic Hypersomnia Severity Scale. Neurology. 2019;92(15):e1754-e1762.

Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, Chandler P, Parvataneni R, Chen D, Skobieranda F, Richard K. Bogan RK. Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of Lower-Sodium Oxybate in Adults With Idiopathic Hypersomnia. Poster No 494, SLEEP 2021, the 35th Annual Meeting of the Associated Professional Sleep Societies (APSS).

Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, Morse AM, Šonka K, Thorpy MJ, Mignot E, Chandler P, Parvataneni R, Black J, Sterkel A, Chen D, Skobieranda F, Bogan RK. Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. Lancet Neurol. 2022;21(1):53-65.

Food and Drug Administration (FDA), Assessment of Abuse Potential of Drugs. (January 2017). Guidance for Industry, U.S. Department of Health and Human Services, Center for Drug Evaluation and Research.

Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (March 2020; updated August 30, 2021).

Guy, W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Department of Health, Education, and Welfare Publication (ADM). Rockville, MD: National Institute of Mental Health, 1976, p 217-222.

Hayashi M, Motoyoshi N, Hori T, Recuperative Power of a Short Daytime Nap With or Without Stage 2 Sleep. Sleep 28(7),829–836, 2005.

Hays RD, Spritzer KL, Schalet BD, Cella D. PROMIS®-29 v2.0 profile physical and mental health summary scores. Qual Life Res. 2018;27(7):1885-1891.

Honda Y, Hishikawa Y, Takahashi Y. Long term treatment of narcolepsy with

methylphenidate (Ritalin). Curr Ther Res. 1979;25(2):288–298.

Inoue Y, Tabata T, Tsukimori N. Efficacy and safety of modafinil in patients with idiopathic hypersomnia without long sleep time: a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study. Sleep Med. 2021;80:315-321.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-545.

Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5-11.

Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y, Haratani T, Fukasawa K. Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol. 2006;117(7):1574-81.

Lawrence G, Muza R. Assessing the sleeping habits of patients in a sleep disorder centre: a review of sleep diary accuracy. J Thorac Dis. 2018;10(Suppl 1):S177-S183.

Lawrence J, Hung, HMJ. Estimation and confidence intervals after adjusting the maximum information. Biometrical Journal. 2003;45(2):143-152.

Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999;55:1286-1290.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

Mallinson DC, Kamenetsky ME, Hagen EW, Peppard PE. Subjective sleep measurement: comparing sleep diary to questionnaire. Nat Sci Sleep. 2019;11:197-206.

Martínez-Martín P, Rodríguez-Blázquez C, Mario Alvarez, Arakaki T, Arillo VC, Chaná P, Fernández W, Garretto N, Martínez-Castrillo JC, Rodríguez-Violante M, Serrano-Dueñas M, Ballesteros D, Rojo-Abuin JM, Chaudhuri KR, Merello M. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. Parkinsonism Relat Disord. 2015;21(1):50-54.

Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med 2021;17:1895–1945.

Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time--a randomized, double-blind, placebo-controlled study. J Sleep Res. 2015;24(1):74-81.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statistics in Medicine. 2011;30(28),3267-3284.

Mitler MM. Evaluation of treatment with stimulants in narcolepsy. Sleep. 1994;17(8 Suppl):S103–S106.

Mitler MM and O'Malley MB. Wake-Promoting Medications: Efficacy and Adverse Effects. p 484-498, in Principles and Practice of Sleep Medicine, 4th ed. Kryger M, Roth T,

Dement WC (eds). Elsevier. Philadelphia, 2005.

Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, Myers MG, Ogedegbe G, Schwartz JE, Townsend RR, Urbina EM, Viera AJ, White WB, Wright JT Jr. Measurement of Blood Pressure in Humans: A Scientific Statement From the American Heart Association. Hypertension. 2019 May;73(5):e35-e66.

Oriyama S and Miyakoshi Y. The effects of nighttime napping on sleep, sleep inertia, and performance during simulated 16 h night work: A pilot study. Journal of Occupational Health. 2018; 60:172-181.

Parasrampuria DA, Schoedel KA, Schuller R, Gu J, Ciccone P, Silber SA, Sellers EM. Assessment of pharmacokinetics and pharmacodynamic effects related to abuse potential of a unique oral osmotic-controlled extended-release methylphenidate formulation in humans. J Clin Pharmacol. 2007;47(12):1476-1788.

Pascoe M, Bena J, Foldvary-Schaefer N. Effects of pharmacotherapy treatment on patient-reported outcomes in a narcolepsy and idiopathic hypersomnia cohort. J Clin Sleep Med. 2019;15(12);1799-1806.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-1277.

Rassu AL, Evangelista E, Barateau L, Chenini S, Lopez R, Jaussent I, Dauvilliers Y. Idiopathic Hypersomnia Severity Scale to better quantify symptoms severity and their consequences in idiopathic hypersomnia. J Clin Sleep Med. 2022;18(2):617-629.

Reed DL, Sacco WP. Measuring Sleep Efficiency: What Should the Denominator Be? J Clin Sleep Med. 2016;12(2):263-266.

Reinish LW, MacFarlane JG, Sandor P, Shapiro CM. REM changes in narcolepsy with selegiline. Sleep. 1995;18(5):362–367.

Ritalin® US Prescribing Information. Novartis Pharmaceuticals Corporation, 2021.

Ritalin LA® US Prescribing Information. Novartis Pharmaceuticals Corporation, 2021.

Ross AJ, Medow MS, Rowe PC, Stewart JM. What is brain fog? An evaluation of the symptom in postural tachycardia syndrome. Clin Auton Res. 2013;23(6):305-311.

Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-1394.

Schneider L, Stevens M, Husain AM, Ito D, Macfadden W, Bujanover S, Fuller DS, Zee P. Impairment in functioning and quality of life in patients with Idiopathic Hypersomnia: the Real World Idiopathic Hypersomnia Outcomes Study (ARISE). Poster presentation at the US Psych Congress, October 29-November 1, 2021a; San Antonio, TX.

Schneider L, Stevens M, Husain AM, Ito D, Macfadden W, Bujanover S, Fuller DS, Zee P. Symptom severity and treatment satisfaction in patients with Idiopathic Hypersomnia: the Real World Idiopathic Hypersomnia Outcomes Study (ARISE). Poster presentation at the US Psych Congress, October 29-November 1, 2021b; San Antonio, TX.

Sellers EM, Romach MK. Categorization of Abuse Potential-Related Adverse Events. Clin Pharmacol Drug Dev. 2018;7(6):569-574.

Shapiro CM, Auch C, Reimer M, Kayumov L, Heslegrave R, Huterer N, Driver H, and Devins GM. A new approach to the construct of alertness. Journal of Psychosomatic Research, 2006;60(6), 595–603.

Swanson JM, Volkow ND. Serum and brain concentrations of methylphenidate: implications for use and abuse. Neurosci Biobehav Rev. 2003;27(7):615-621.

Takahashi M, Arito H. Maintenance of alertness and performance by a brief nap after lunch under prior sleep deficit. Sleep. 2000;23(6):813-819.

Tang E, Ekundayo O, Peipert JD, Edwards N, Bansal A, Richardson C, Bartlett SJ, Howell D, Li M, Cella D, Novak M, Mucsi I. Validation of the Patient-Reported Outcomes Measurement Information System (PROMIS)-57 and -29 item short forms among kidney transplant recipients. Qual Life Res. 2019;28(3):815-827.

Thakrar C, Patel K, D'ancona G, Kent B, Nesbitt A, Selsick H, Steier J, Rosenzweig I, Williams AJ, Leschziner GD, Drakatos P. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. J Sleep Res. 2018:27(4):e12627.

Trenque T, Herlem E, Abou Taam M, Drame M. Methylphenidate off-label use and safety. sleepiness Springerplus. 2014;3:286-.

Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in γ-aminobutyric acid-Related hypersomnolence: A randomized, crossover trial. Ann Neurol. 2015;78(3):454-465.

Trotti LM, Saini P, Koola C, LaBarbera V, Bliwise DL, Rye DB. Flumazenil for the Treatment of Refractory Hypersomnolence: Clinical Experience with 153 Patients. J Clin Sleep Med. 2016;12(10):1389-1394.

Trotti LM, Ong JC, Plante DT, Friederich Murray C, King R, Bliwise DL. Disease symptomatology and response to treatment in people with idiopathic hypersomnia: initial data from the Hypersomnia Foundation registry. Sleep Med. 2020;75:343-349.

Van Balen EC, Haverman L, Hassan S, Taal EM, Smit C, Driessens MH, Beckers EAM, Coppens M, Eikenboom J, Hooimeijer HL, Leebeek FWG, van Vulpen LFD, Schols SEM, Terwee CB, Rosendaal FR, van der Bom JG, Gouw SC. Validation of PROMIS Profile-29 in adults with hemophilia in the Netherlands. J Thromb Haemost. 2021 Nov;19(11):2687-2701.

Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. J Sleep Res. 2010;19(4):525-534.

Viktrup L, Hayes RP, Wang P, Shen W. Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. BMC Urology. 2012;12:30.

Watson NF, Davis CW, Zarycranski D, Vaughn B, Dayno JM, Dauvilliers Y, Schwartz JC.

Time to Onset of Response to Pitolisant for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Patients With Narcolepsy: An Analysis of Randomized, Placebo-Controlled Trials. CNS Drugs. 2021;35(12):1303-1315.

Xywav US Prescribing Information. Jazz Pharmaceuticals, Palo Alto, CA, 2021.

Yoss RE, Daly DD. Treatment of narcolepsy with Ritalin. Neurology. 1959;9(3):171-173.

Appendix A: Change in events when site visits must be converted to remote visits

Assessment (Per Section 1)	Conduct remotely (telephone or videoconference)	Mail/Deliver to subject, as applicable	Perform when the subject is able to safely return to an on-site visit
Inclusion/Exclusion	X		
Medical History	X		
Physical Examination			X
Body Weight			X
Vital Signs			X
12-Lead ECG			X
Chemistry/Hematology/ Urinalysis			X
Pregnancy Test		X	
C-SSRS			X
Retrieve/Dispense Study Drug	X [a]	X	X [a]
ESS	X		
PGI-S	X		
CGI-S	X		
IHSS	X		
Brain Fog Scale	X		
PROMIS®-29	X		
ZOGIM-A	X		
Review of Sleep Inertia VAS (SIVAS)	X [b]		
Review of Mod-KSS	X [b]		
Review of Sleep Diary	X [b]		
Review of Dosing Diary	X		
Adverse Events	X		
Concomitant Medications	X		

a. Sites will discuss with the subject the amount of study drug taken and the amount remaining in bottles at the time of the telephone/videoconference visits. Final compliance calculations will be made at the next on-site visit when the bottles are retuned.

b. Sites will review the SIVAS, Mod-KSS, and Sleep Diaries during the telephone/ videoconference visits to ensure completeness.

Appendix B: ICSD-3 Criteria for Diagnosis of Idiopathic Hypersomnia (IH)

All 6 criteria listed below (a to f) need to be satisfied for a diagnosis of IH.

a) Subject has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

b) Cataplexy is absent.

c) A multiple sleep latency test (MSLT) performed according to standard techniques shows fewer than 2 "Sleep Onset REM Periods" (SOREMPs) or no SOREMPs if the REM latency on the preceding polysomnogram (PSG) was ≤15 minutes.

d) The presence of at least 1 of the following:

- The MSLT shows a mean sleep latency of ≤8 minutes.
- Total 24-hour sleep time is ≥660 minutes on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation) , or by wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep).

e) Insufficient sleep syndrome is ruled out.

f) The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

Source: American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders, 3rd ed (ICSD-3). Darien, IL: 2014.

Appendix C: Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

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, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

Appendix D: Brain Fog Questionnaire

"Brain Fog" Questionnaire (Part 1 – Frequency)

"Brain Fog" is a term used for certain symptoms that can affect your ability to think and function. Symptoms include a lack of mental clarity; and a feeling of being mentally sluggish and fuzzy, leading to forgetfulness, mental cloudiness, and difficulty focusing, thinking and communicating.

1. How many days did you experience "Brain Fog" during the last week? Please check one.

   Never ☐
   Once ☐
   2-3 Days ☐
   4-6 Days ☐
   Every day ☐

   If you experienced "Brain Fog" last week, please answer the remaining questions below.

2. How frequent did you experience "Brain Fog", on average during the day? Please check one.

   Once per day ☐
   A few hours per day ☐
   Most of the day ☐
   All day ☐

3. When was your "Brain Fog" most severe? Please check one.

   First hour after awakening ☐
   Morning ☐
   Afternoon ☐
   Evening ☐
   No pattern/fluctuating ☐

4. What activities were impaired by your "Brain Fog"? Please check one.

   None ☐
   Social activities ☐
   Work/school activities ☐
   All activities ☐

5. If activities were impaired by "Brain Fog", when was the impairment most severe? Please check one.

First hour after awakening	☐
Morning	☐
Afternoon	☐
Evening	☐
No pattern/fluctuating	☐

"Brain Fog" Questionnaire (Part 2 – Severity)

Question: How severe was your impairment because of "Brain Fog" during the last week? Please circle one number.

0	10	20	30	40	50	60	70	80	90	100
Not at all severe										**Extremely severe**

"Brain Fog" Questionnaire (Part 3 - Descriptors)

Please check which describes your mental state while experiencing "Brain Fog" during the last week. Check one for each item.

	Strongly Agree (4)	Agree (3)	Neutral (2)	Disagree (1)	Strongly Disagree (0)
1. Forgetful	☐	☐	☐	☐	☐
2. Difficulty thinking	☐	☐	☐	☐	☐
3. Difficulty focusing	☐	☐	☐	☐	☐
4. Cloudy	☐	☐	☐	☐	☐
5. Difficulty finding the right words/ communicating	☐	☐	☐	☐	☐
6. Mental fatigue	☐	☐	☐	☐	☐
7. Slow	☐	☐	☐	☐	☐
8. Mind went blank	☐	☐	☐	☐	☐
9. Spacey	☐	☐	☐	☐	☐
10. Difficulty processing what others say	☐	☐	☐	☐	☐
11. Exhausted	☐	☐	☐	☐	☐
12. Easily distracted	☐	☐	☐	☐	☐
13. Difficulty processing words read	☐	☐	☐	☐	☐
14. Confused	☐	☐	☐	☐	☐
15. Annoyed	☐	☐	☐	☐	☐
16. Sleepy	☐	☐	☐	☐	☐
17. Lost	☐	☐	☐	☐	☐
18. Detached	☐	☐	☐	☐	☐
19. Thoughts moving too quickly	☐	☐	☐	☐	☐

Thank you for completing this questionnaire

Appendix E: Clinical Global Impression of Severity (CGI-S)

Clinical Global Impression of Severity (CGI-S)

Check if Not Done ☐

(Choose only one)

CGI - SEVERITY

Considering your total clinical experience with this patient population, how ill is the patient at this time?

☐ 1. Normal, not at all ill

☐ 2. Borderline ill

☐ 3. Mildly ill

☐ 4. Moderately ill

☐ 5. Markedly ill

☐ 6. Severely ill

☐ 7. Among the most extremely ill patient

Appendix F: Patient Global Impression of Severity (PGI-S)

Patient Global Impression of Severity (PGI-S)

Check if Not Done ☐

(Choose only one)

PGI - SEVERITY

How would you describe your overall disease condition over the past week?

☐ 1. Not present

☐ 2. Very mild

☐ 3. Mild

☐ 4. Moderate

☐ 5. Moderately severe

☐ 6. Severe

☐ 7. Extremely severe

Appendix G: Idiopathic Hypersomnia Severity Scale (IHSS)

IDIOPATHIC HYPERSOMNIA SEVERITY SCALE

Considering your symptoms during the past seven days:

1. What for you is the ideal duration of night-time sleep *(at the weekend or on holiday, for example)?*

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

2. When circumstances require that you get up at a particular time in the morning *(for example for work or studies, or to take the children to school during the week)*, do you feel that 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 in the morning without several alarm calls or the help of someone close?

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

4. After a night's sleep, how long does it take you to feel you are functioning properly after you get up *(in other words fully functional, both physically and intellectually)*?

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 I am functioning properly as soon as I wake up

5. In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy *(for example, tripping up, breaking things or dropping 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 a week)
3 ❑ often (4-5 times a week)
2 ❑ sometimes (2-3 times a week)
1 ❑ rarely (once a week)
0 ❑ never

7. What for you is the ideal length of your naps *(at the weekend or on holiday, for example)?*
☞ *Note: If you take several naps, add them all together*

3 ❒ 2 hours or more
2 ❒ more than 1 hour and less than 2 hours
1 ❒ less than 1 hour
0 ❒ no naps

8. In general, how do you feel after a nap?

3 ❑ very sleepy 2 ❑ sleepy 1 ❑ awake 0 ❑ wide awake

9. During the day, while carrying out 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 a week)
2 ❑ sometimes (2-3 times a week)
1 ❑ rarely (once a week or less)
0 ❑ never

10. Do you consider that your hypersomnolence has an impact on your general health (*i.e. lack of energy, no motivation to do things, physical fatigue on exertion, decrease in physical fitness)*?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no impact

11. Do you consider that your hypersomnolence is a problem in terms of your proper intellectual functioning *(i.e. problems with concentration, memory problems, decrease in your intellectual performance)*?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no problem

12. Do you consider that your hypersomnolence affects your mood *(for example sadness, anxiety, hypersensitivity, irritability)*?

4 ❒ very severely 3 ❒ severely 2 ❒ moderately 1 ❒ slightly 0 ❒ not at all

13. Do you consider that your hypersomnolence prevents you from carrying out daily tasks properly *(family-related or household tasks, school, leisure or job-related tasks)*?

4 ❒ very significantly 3 ❒ significantly 2 ❒ moderately 1 ❒ slightly 0 ❒ not at all

14. Do you consider that your hypersomnolence is a problem in terms of your driving a car?

4 ❒ very significant 3 ❒ significant 2 ❒ moderate 1 ❒ minor 0 ❒ no problem
❒ I do not drive

Appendix H: Modified Karolinska Sleepiness Scale (Mod-KSS)

Subjects will complete the Mod-KSS twice per day, once at approximately 1 hour after awakening (morning) and once at approximately 6 pm (late afternoon). The following instructions will be provided for each daily assessment:

Morning Mod-KSS Instructions:
Please complete daily at approximately 1 hour after awakening.
Select one score that indicates how you feel today during the first hour after awakening.

Late Afternoon Mod-KSS Instructions:
Please complete daily at approximately 6 pm.
Select one score that indicates how you feel between 5 pm and 6 pm today.

Modified Karolinska Sleepiness Scale (Mod-KSS)

Extremely alert	☐ 1
Very alert	☐ 2
Alert	☐ 3
Rather alert	☐ 4
Neither alert nor sleepy	☐ 5
Some signs of sleepiness	☐ 6
Sleepy, but no effort to keep awake	☐ 7
Sleepy, but some effort to keep awake	☐ 8
Very sleepy, great effort to keep awake, fighting sleep	☐ 9
Extremely sleepy, can't keep awake	☐ 10

Score 10 is an additional score in the "modified" version:

Appendix I: PROMIS-29® Profile v2.1

Included Domains: Emotional Distress-Depression, Fatigue, and Ability to Participate in Social Roles and Activities (PROMIS© Item Bank v1.0 – Short Form 4a).

Please respond to each question or statement by marking one box per row based on how you felt over the past week.

	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

10 July 2018

Appendix J: ZOGIM-A (Alertness Questionnaire)

This brief questionnaire deals with your level of alertness. Use the following scale to check one response for each question based on how you felt over the past week.

Alertness can be affected by different experiences. How might your alertness be affected by each of the following?	Not at all 5	Slightly 4	Moderately 3	Largely 2	Extremely 1
a. Losing about 30 min of nighttime sleep.					
b. Doing about 30 min of exercise.					
c. Not drinking coffee or other foods that contain caffeine.					
d. Taking a 1-week vacation.					
e. Forgetting about your worries.					
If you were more alert	Not at all 5	Slightly 4	Moderately 3	Largely 2	Extremely 1
a. Would you be able to organize your day-to-day activities more effectively?					
b. Would you be able to complete your tasks more methodically?					
c. Would your new ideas occur to you more readily?					
d. Would you make fewer careless mistakes?					
e. What proportion of the day do you feel a high level of alertness?	5 90-100%	4 50-90%	3 10-15%	2 0-15%	1 0%

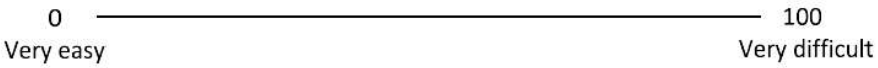
From Shapiro CM, Auch C, Reimer M, Kayumov L, Heslegrave R, Huterer N, Driver H, and Devins GM (2006). A new approach to the construct of alertness. Journal of Psychosomatic Research, 60 (6), 595–603.

Appendix K: Visual Analog Scale for Sleep Inertia

Visual Analog Scale for Sleep Inertia

Please complete daily at approximately 1 hour after awakening.
Mark the horizontal line with an X at a place that indicates your score.

How difficult was it for you to wake up this morning?



Appendix L: Sleep Diary

Morning Part of the Sleep Diary (questions about last night):

Please complete shortly after awakening

Example

Today's Date:	28-Feb-22	
Questions 1-7 refer to your sleep last night		
1. What time did you get into bed?	9:55 pm	
2. What time did you try to go to sleep?	10:30 pm	
3. How long did it take you to fall asleep?	20 min	
4. How many times did you wake up, not counting your final awakening?	2 times	
5. In total, how long did these awakenings last? (mins)	30 min	

6. Was there anyting unusual that affected your sleep?	☐ Yes ☐ No ☒ Illness ☐ Unusually noisy environment ☐ Someone woke me ☐ Unusual activities ☐ Other .I have a cold	☐ Yes ☐ No ☐ Illness ☐ Unusually noisy environment ☐ Someone woke me ☐ Unusual activities ☐ Other ……..
Questions 7-9 refer to your wake-up today		
7. What time was your final awakening?	7:00 am	
8. What time did you get out of bed for the day?	7:45 am	
9. Is today an off day (non working day)?	☐ Yes ☒ No	☐ Yes ☐ No

Evening Part of the Sleep Diary (questions about today):

Please complete before going to sleep tonight.

Example

Today's Date:	28-Feb-22	
Questions 10-12 refer to your nap(s) today		
10. How many times did you nap or doze today?	2 times	
11. In total, how long did you nap or dose duirng the day? (add all naps if you had more than 1) (mins)	70 min	
12. Was there anyting unusual about your naps tody? If YES, please explain	☐ Illness ☒ Unusually noisy environment ☐ Someone woke me ☐ Unusual activities ☐ Other ….	☐ Illness ☐ Unusually noisy environment ☐ Someone woke me ☐ Unusual activities ☐ Other ….

General Instructions for Sleep Diary:

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. There will be questions for you to answer first thing in the morning and additional questions to answer before going to sleep for the night. The sleep diary should be completed within one hour after awakening in the morning, and again at night just before going to sleep.

When do I complete the sleep diary? What should I do if I forget to complete the sleep diary?

- Morning: The first trigger for the morning part of the sleep diary will occur at 5 AM; you can ignore that if you are still asleep, and it will not wake you up. It is best to complete the morning part of the sleep diary approximately 1 hour after your awakening because you will be able to answer all morning questions (morning sleepiness feelings, and waking-up difficulty). However, if you forget or are unable to complete the morning part of the sleep diary when you wake up, you will have until 11 AM to answer the questions. After the last trigger at 11 AM, the morning part of the sleep diary for that day will not be available anymore.
- Evening: The best time to complete the evening part of the sleep diary is just before wanting to go to sleep, because you will be able to complete all evening questions at the same time. The first trigger for the evening part of the sleep diary will occur at 6 PM and the last trigger will occur at 2 AM. If you are not going to sleep early, please ignore the early triggers. The triggers will stop after you completed all questionnaires, so that they will not wake you up after going to sleep. After the last trigger at 2 AM, the evening part of the sleep diary for that day will not be available anymore.

What do the words "bed," "night" and “day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word night is the time when you choose to go to bed, and the word day is the time when you choose or are required to be awake. The term “bed” means the place where you usually sleep.

Please note that the time of going to sleep is the time that you intent to be the start of your nighttime sleep, and it is not necessary the same as your bedtime since you may go to bed and intentionally stay awake, to watch TV, for example. Instead, the time of going to sleep is the time of lights out, electronic devices silenced, etc.

Similarly, the time of awakening is not necessary the same as the time of getting out of bed since you might check your messages or call someone, for example, after awakening but before getting out of bed. Your time of awakening is the time that you intent to be awake. You might use an alarm clock for this, for example.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Sleep Diary Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary.

1. *What lime time you get into bed?* Write the time that you got into bed last night. This may not be the time you began "trying" to fall asleep.

2. *What time did you try to go to sleep?* Record the time that you began "trying" to fall asleep for the night.
   If you went to bed with the intention to go asleep right away, this is time that you went to bed. Do not include the time in bed while performing other activities (watching TV, for example).
   If you fell asleep unintentionally (for example, on the couch) but it became your nighttime sleep or part of your nighttime sleep (meaning, it was not a short doze), report the time that you fell asleep unintentionally.

3. *How long did it take you to fall asleep?* Beginning at the time you wrote in question 1, how long did it take you to fall asleep. If you fell asleep for the night unintentionally, answer 0 (zero) minutes.

4. *How many times did you wake up, not counting your final awakening?* Please record how many times you woke up between the time you first fell asleep, and the time of your final awakening.

5. *In total, how long did these awakenings last?* What was the total time you were awake between the lime you first fell asleep and your final awakening? For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20 min + 35 min + 15 min = 70 min or 1 hr and 10 min).

6. *Was there anything unusual that affected your sleep last night? (Yes/No) If yes, please, explain.* Please mark yes if there were unusual circumstances that affect your sleep (e.g., illness, unusually noisy environment, someone woke you, unusual activities or occasions that impacted your normal sleep.)

7. *What time was your final awakening?* Record the last time you woke up in the morning. This is the time you woke up with no further attempt at sleeping. This does not include the time that you stayed in bed after your final awakening (for example, you may have checked your phone while in bed after awakening).
   If you woke up because your alarm went off and you wanted to wake up but had trouble getting up right away, report the time of the first attempt to wake up. If you woke up because

your alarm went off but went back to sleep (e.g., you may have planned to snooze), report the time that you woke up with no further attempts at sleeping.

8. What time did you get out of bed for the day? What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g., you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:00 a.m.)

9. *Is today an off day (e.g., non-working day/weekend or holiday)?* An off day is a day when you are not required or scheduled to do activities. If you are employed, this is usually your day off. However, you may have other scheduled activities in your day (e.g., getting your children to school) that would make the day count as a workday.

10. *How many times did you nap or doze during the day?* A nap is a time you decided to sleep during the day, whether in bed or not in bed. "Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you napped or dozed at any time from when you first got out of bed in the morning until you got into bed again at night.

11. *In total, how long did you nap or doze during the day?* Estimate the total amount of time you spent napping or dozing, in hours and minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes." If you did not nap or doze, write "N/A" (not applicable).

12. *Was there anything unusual about your naps today? (Yes/No) If yes, please explain.* Please mark yes if there were unusual circumstances that affect your sleep (e.g., illness, unusually noisy environment, unusual activities or occasions that impacted your normal sleep.)

The Sleep Diary used in this study a based on The Consensus Sleep Diary: Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.

Appendix M: Dosing Diary

Subjects will complete the Dosing Diary at night after taking the evening dose for subjects receiving the qd pm dosing regimen; and in the evening and morning after taking the respective doses for subjects receiving the bid dosing regimen.

The following questionnaire will be provided for each daily assessment, as appropriate:

Morning Dosing Diary:

Please complete daily at approximately 1 hour after awakening:

At what time did you take your morning dose of study drug? _____ AM ☐ PM ☐
Did you eat a meal within 1 hour before or 1 hour after taking your study drug this morning? Yes ☐ No ☐

Evening Dosing Diary:

Please complete daily before going to sleep for the night:

At what time did you take your evening dose of study drug? _____ AM ☐ PM ☐
Did you eat a meal within 1 hour before or 1 hour after taking your study drug this evening? Yes ☐ No ☐

Appendix N: Question #6 of the Pittsburgh Sleep Quality Index (PSQI)

Instructions:

The following question relates to your usual sleep habits during the past 2 weeks only. Your answer should indicate the most accurate reply for the majority of days and nights in the past 2 weeks.

"During the past 2 weeks, how would you rate your nighttime sleep quality overall?"

Check only one answer.

☐ 0. Very good

☐ 1. Fairly good

☐ 2. Fairly bad

☐ 3. Very bad

Source: Question #6 of the Pittsburgh Sleep Quality Index (PSQI): Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research 1989;28(2):193-213.

Appendix O: Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

	Lifetime: Time He/She Felt Most Suicidal	Past 12 Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having 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 ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)

Past X Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)

	Most Severe	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	____	

C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 5 Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

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

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

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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **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* _____

Appendix P: Antidepressants With and Without Sedating Effects

Antidepressants with Sedating Effects (Prohibited)		Antidepressants without Sedating Effects (Allowed)	
Tricyclics	Amitriptyline Amoxapine Clomipramine Doxepin Imipramine Maprotiline Trimipramine Desipramine Nortriptyline Protriptyline	SSRIs	Escitalopram Fluoxetine Paroxetine Sertraline
		SNRI	Desvenlafaxine Levomilnacipran Milnacipran Venlafaxine
		NRI	Atomoxetine
		NDRI	Bupropion
SSRIs	Citalopram Duloxetine Fluvoxamine	MMADs	Vilazodone Vortioxetine
Atypical/novel	Mirtazapine Trazodone Brexanolone Esketamine		

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; NRI = norepinephrine reuptake inhibitor; NDRI = norepinephrine-dopamine reuptake inhibitor; MMAD = multimodal antidepressant

From: Schweitzer PK. Hypersomnia Due to a Medication or Substance. In: Reference Module in Neuroscience and Biobehavioral Psychology. Elsevier, 2021.