Official Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pitolisant on Excessive Daytime Sleepiness and Other Non-Muscular Symptoms in Patients with Myotonic Dystrophy Type 1, Followed by an Open-Label Extension

NCT Number: NCT04886518

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

CLINICAL STUDY PROTOCOL: HBS-101-CL-005

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pitolisant on Excessive Daytime Sleepiness and Other Non-Muscular Symptoms in Patients with Myotonic Dystrophy Type 1, Followed by an Open-Label Extension
Investigational Product:	Pitolisant (also referred to as HBS-101)
Phase of Development:	2
Sponsor:	Harmony Biosciences, LLC 630 W. Germantown Pike, Suite 215 Plymouth Meeting, PA 19462 USA
Medical Monitor:	[redacted]
Operational Lead:	[redacted]
Protocol Amendment:	Amendment 5
Effective Date:	18JUL2023

SPONSOR SIGNATURE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pitolisant on Excessive Daytime Sleepiness and Other Non-Muscular Symptoms in Patients with Myotonic Dystrophy Type 1, Followed by an Open-Label Extension
Protocol Number:	HBS-101-CL-005

This protocol Amendment 5 has been reviewed and approved by the Sponsor.

Signatur [redacted] Date: [redacted]

[redacted]

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

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HBS-101-CL-005

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pitolisant on Excessive Daytime Sleepiness and Other Non-Muscular Symptoms in Patients with Myotonic Dystrophy Type 1, Followed by an Open-Label Extension

I have received and read the current Investigator's Brochure for pitolisant. I have read the HBS-101-CL-005 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Confidentiality Statement

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Harmony Biosciences, LLC
NAME OF FINISHED PRODUCT(S):	Pitolisant tablets (also referred to as HBS-101)
NAME OF ACTIVE INGREDIENT(S):	Pitolisant hydrochloride (also referred to as HBS-101)
PROTOCOL NUMBER:	HBS-101-CL-005
PHASE OF DEVELOPMENT:	2
PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pitolisant on Excessive Daytime Sleepiness and Other Non-Muscular Symptoms in Patients with Myotonic Dystrophy Type 1, Followed by an Open-Label Extension	
NUMBER OF PLANNED SUBJECTS: 30	
STUDY SITES: Approximately 22 sites in the United States (US) and Canada	

STUDY OBJECTIVES:

Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of pitolisant compared with placebo in treating excessive daytime sleepiness (EDS) in patients with myotonic dystrophy type 1 (DM1) ages 18 to 65 years.

Secondary Objectives

The secondary objectives of this study are to assess:

- the impact of pitolisant on fatigue in patients with DM1
- the impact of pitolisant on selected domains of cognitive function in patients with DM1
- investigator and patient impression of overall impact of pitolisant on burden of disease in patients with DM1
- safety and effectiveness of pitolisant during long-term treatment (during the Open-Label Extension [OLE] Phase)

METHODOLOGY:

Double-Blind, Placebo-Controlled Treatment Phase:

After completion of the Screening Period, eligible patients who agree to participate will be randomized in a 1:1:1 ratio to one of three treatment groups: lower dose pitolisant (17.8 mg), higher dose pitolisant (35.6 mg), or placebo. Study drug doses will be titrated during a 3-week period (Day 1 to 21):

- Pitolisant lower dose 17.8 mg treatment group: Week 1 (Day 1-7), 4.45 mg; Week 2 (Day 8-14), 8.9 mg; Week 3 (Day 15-21), 17.8 mg
- Pitolisant higher dose 35.6 mg treatment group: Week 1 (Day 1-7), 8.9 mg; Week 2 (Day 8-14), 17.8 mg; Week 3 (Day 15-21), 35.6 mg
- Patients randomized to placebo will receive matching doses of placebo tablets over the 3-week Titration Period and during the Stable Dose Period.

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

Efficacy assessments will be performed at the Baseline Visit (Day -1), Visit 4 (Day 49), and Visit 5 (Day 77), with the exception of the optional Maintenance of Wakefulness Test (MWT), Cogstate Computerized Cognitive Battery Tests and Sustained Attention to Response Task (SART), which are

only to be performed at the Baseline and End of Treatment (EOT) study visits. At the end of the Double-Blind Treatment Phase (Day 77/Visit 5), patients who do not enter the optional OLE Phase will have two safety follow-up telephone contacts (TCs), one 15 (±3) days and another 30 (+3) days after the final dose of blinded treatment.

Safety assessments will include electrocardiograms (ECGs; in triplicate) at Screening, Baseline, Day 22 (Visit 3), Day 49 (Visit 4), and Day 77 (Visit 5). In addition to ECG testing, Holter monitoring will be performed during Screening and at Visit 3 (Day 22). On those days when a Holter monitor is placed on the patient, the ECG data will be taken from the Holter monitor recording. Any clinically significant finding from Holter monitoring requires additional evaluation (including an unscheduled ECG). Adverse event (AE) and concomitant medication monitoring and Columbia-Suicide Severity Rating Scale (C-SSRS) assessment will be conducted at all visits whether on-site or by TC. Patients will receive TCs from the site on Days 8, 15, and 28.

During the Double-Blind Treatment Phase, patients will undergo pharmacokinetic (PK) assessments at the study site on Day 22 (Visit 3) and at the end of the double-blind treatment on Day 77 (Visit 5). For on-site study visits with PK sampling, patients will be instructed to not take their study drug in the morning upon wakening; rather, study drug administration will be held until the patient is at the study site, and timing of dose administration will be based on the PK sampling schedule.

Open-Label Extension Phase:

For patients who elect to enter the OLE Phase of the study, eligibility criteria will be confirmed at the EOT Visit/Day 77 (Visit 5) in the Double-Blind Treatment Phase. Patients must complete the Double-Blind Treatment Phase of the study to be eligible to participate in the optional OLE Phase of the study.

All eligible patients who enter the OLE Phase will receive open-label pitolisant that will be titrated to a dose of 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability):

- Week 12 (Day 78-84), 8.9 mg
- Week 13 (Day 85-91), 17.8 mg
- Week 14 (Day 92-98), 35.6 mg

After completion of the Titration Period in the OLE Phase, patients will continue to receive open-label pitolisant at 35.6 mg (or their maximum dose up to 35.6 mg based on Investigator assessment of tolerability) and will be instructed to take their study drug once daily in the morning upon wakening.

Patients will receive TCs from the site on Day 85/Week 13 and Day 92/Week 14 during the OLE Titration Period to assess AEs (including cardiovascular [CV] symptoms and psychiatric events), and concomitant medication use, complete the C-SSRS and to confirm titration of pitolisant. On Day 99/Visit 6, patients will return to the site to complete safety and effectiveness assessments; 24-hour Holter monitoring will be initiated at this visit (a clinically significant finding from Holter monitoring requires additional evaluation, including an unscheduled ECG). A telephone visit will occur 3 months later on Day 189/Month 6 followed by an on-site study visit (Visit 7) 3 months later (Day 279/Month 9). Another telephone visit will occur 3 months later, on Day 369/Month 12. All patients who complete the study will have an End of Treatment (EOT) visit at Day 459/Month 15 (Visit 8). If the patient withdraws from the study early or the study is terminated by the Sponsor, every effort should be made to conduct an EOT or Early Termination Visit.

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

At all on-site study visits (approximately every 6 months), safety assessments (including full physical examination, body weight, clinical laboratory assessments, 12-lead ECGs [in triplicate], vital signs, suicidality assessment [by C-SSRS]), and effectiveness assessments will be performed. If interim CV assessments are required at the discretion of the Investigator, patients will return to the study site for unscheduled visits that will include an ECG. Adverse events and concomitant medication use will be

monitored throughout treatment during all TCs and at all on-site study visits. The C-SSRS will also be completed during TCs by certified individuals. Patients who are treated in the OLE Phase will have two safety follow-up TCs with the study site 15 (±3) days and 30 (+3) days after their final dose of open-label pitolisant, which will include assessment for AEs (including CV symptoms or psychiatric events) and concomitant medication use.

STUDY POPULATION:

Inclusion Criteria

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

1. Is able to provide voluntary, written informed consent.
2. Has a diagnosis of DM1 confirmed by genetic testing (cytosine-thymine-guanine [CTG] repeat of ≥100) from the Screening Visit.
3. Male or female patients ages 18 to 65 years at the time of enrollment.
4. [redacted]
5. If on a wake-promoting treatment that could affect EDS (including stimulants, modafinil, and armodafinil):
   a. Must be on a stable dose for at least 2 months prior to Screening and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase).
   b. If not on a stable dose for 2 months prior to Screening, washout for 5 half-lives prior to randomization and agree to remain off these treatments for the duration of the Double-Blind Treatment Phase of the study.
6. Washout of cannabidiol and tetrahydrocannabinol for 28 days prior to randomization and agree to remain off for the duration of the Double-Blind Treatment Phase of the study.
7. Able to walk independently with or without an assistive device (e.g., cane, walker, orthoses allowed).
8. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test at the Baseline Visit and agree to remain abstinent or use an effective method of non-hormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
9. In the opinion of the Investigator, the patient is capable of understanding and complying with the protocol and administration of oral study drug.

Exclusion Criteria

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

1. Has a diagnosis of another genetic or chromosomal disorder that is distinct from DM1 and that is not being managed adequately in the opinion of the investigator.
2. [redacted]

3. Consistently consumes >600 mg of caffeine per day and is unable/unwilling to reduce caffeine intake to <600 mg per day for the duration of the Double-Blind Treatment Phase of the study; caffeine intake should remain consistent during Screening and throughout the Double-Blind Treatment Phase of the study.
4. Does not agree to discontinue any prohibited medication or substances listed in the protocol (Section 5.7.2).
5. Is currently breastfeeding or planning to breastfeed over the course of the study. Lactating women must agree not to breastfeed for the duration of the study (Double-Blind Treatment Phase and OLE Phase) and for 21 days after final dose of study drug.
6. Participation in an interventional research study involving another investigational medication or device in the 28 days prior to enrollment; patients who undergo a washout of an investigational medication of at least 5 half-lives can be enrolled in the Double-Blind Treatment Phase of the study. Patients considering participation in another interventional research study in the OLE Phase must consult with the Investigator who will consult with the Medical Monitor.
7. Has a primary diagnosis of severe psychiatric illness.
8. Patients taking antidepressants who have not been on a stable dose of their antidepressant for at least 12 weeks prior to Screening; for patients on a stable dose of their antidepressant for at least 12 weeks prior to Screening, must agree to continue their stable dose for the duration of the Double-Blind Treatment Phase of the study. Dose adjustments will be permitted in the OLE Phase. In the Double-Blind Treatment Phase of the study, antidepressants that are strong CYP2D6 inhibitors are exclusionary (Section 5.7.2).
9. Has a history of sleep-disordered breathing or another underlying sleep disorder that in the opinion of the Investigator is a main contributory factor to the patient's EDS.
10. Has a diagnosis of end-stage renal disease (ESRD; estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).
11. Has a diagnosis of moderate or severe renal impairment (eGFR ≥15 to ≤59 mL/minute/1.73 m^2) or moderate hepatic impairment (Child-Pugh B) at Screening or during the Double-Blind Treatment Phase.
12. Has a family history of sudden cardiac death, unexplained death, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member (i.e., first degree relative such as parent, sibling, or offspring).
13. Has a history of unexplained syncope.
14. Has a history of long corrected QT interval (QTc) syndrome or corrected QT interval using Fridericia's formula (QTcF) >450 msec for males or >470 msec for females (QTcF = QT / 3√RR) sustained atrial fibrillation (AF) or left ventricular ejection fraction <50%.
15. Has a history of documented symptomatic arrhythmias (e.g., ECG, Holter monitor).
16. Electrocardiogram abnormalities during a 10-second, 12-lead ECG at Screening of first-degree atrioventricular block (AVB; PR interval >220 msec), QRS >120 msec, heart rate (HR) <50 beats per minute (bpm), marked T-wave abnormalities, more than single atrial premature

complexes (APCs) or premature ventricular contractions (PVCs), left bundle branch block, or Brugada pattern type 1.

Note: Patients with 1st degree AVB with a PR interval ≥220 msec who are treated prophylactically with an allowable implanted device are not excluded from the study.

17. Based on Holter monitor, any episode of 3rd degree AVB, any prolonged episode of second degree AVB (>2 episodes during waking hours, >6 episodes during sleep), any prolonged episode of 2nd degree AVB (>10 seconds), any asystole longer than 3.5 seconds, any run of ventricular tachycardia (VT) >6 beats, frequent runs of non-sustained VT (>5/24 hour), >400 PVCs/24 hours, AF or paroxysmal AF, or frequent or complex atrial arrhythmias.
18. Has history of New York Heart Association (NYHA) class III or class IV heart failure.
19. Has an implanted defibrillator or implanted biventricular pacemaker.

    Note: Patients with implanted univentricular pacemakers that are used prophylactically to prevent or treat bradycardia or heart block may be included.
20. Is receiving a medication known to prolong the QT interval.
21. Has a history of clinically significant hypokalemia or hypomagnesemia that cannot be adequately controlled by supplementation.
22. Has serum potassium or magnesium levels that are outside of the normal reference ranges and considered clinically significant at Screening. Patients with mild hyperkalemia that, in the opinion of the Investigator, does not pose an arrhythmia threat may be included.
23. Is receiving a concomitant medication that is known to be a strong cytochrome P450 (CYP) 2D6 inhibitor, a strong CYP3A4 inducer, or a centrally acting histamine 1 receptor (H_1R) antagonist (sedating antihistamine).

    Note: Patients who undergo a washout of these medications of at least 5 half-lives may be enrolled in the Double-Blind Treatment Phase of the study.
    Note: Use of strong CYP2D6 inhibitors and strong CYP3A4 inducers is allowed during the OLE Phase; however, adjustment of pitolisant dose is required (Section 3.1.2.2). Although not prohibited during the OLE Phase of the study, use of centrally acting or sedating H_1R antagonists should be avoided.
24. Is a known CYP2D6 poor metabolizer (PM).
25. Regular use (more than twice per week) of any sleep-promoting treatments that could affect EDS and not willing to limit use to no more than twice per week during Screening and for the duration of the Double-Blind Treatment Phase of the study (use of sleep-promoting agents are not allowed within one day prior to study-related assessments).
26. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.

27. Has initiated any new or change in allied health therapies or interventions that can interfere with the study outcomes within 28 days prior to randomization and that are prohibited during the Double-Blind Treatment Phase of the study, based on the Investigator's judgment.
28. Has a current or recent (within 1 year) history of a substance use disorder or dependence disorder, including alcohol and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).
29. Has planned surgery during the Double-Blind Treatment Phase of the study; planned surgery is permitted during the OLE Phase.
30. Has a significant risk of committing suicide or suicidality based on history, routine psychiatric examination, Investigator's judgment, or who has an answer of "yes" on any question other than questions 1 to 3 on the C-SSRS (Appendix C).
31. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to an unstable or uncontrolled medical condition or one that might interfere with the conduct of the study, confound interpretation of study results, pose a health risk to the patient, or compromise the integrity of the study.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Pitolisant will be provided as 4.45 mg and 17.8 mg tablets.

Pitolisant will be administered orally as a single dose of lower dose pitolisant (17.8 mg) or higher dose pitolisant (35.6 mg) once daily in the morning upon wakening in the Double-Blind Treatment Phase, and 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability) once daily in the morning upon wakening in the OLE Phase.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Placebo will be provided as matching 4.45 mg and 17.8 mg tablets in the Double-Blind Treatment Phase, administered orally once daily in the morning upon wakening.

DURATION OF TREATMENT:

The duration of the study for each patient in the Double-Blind, Placebo-Controlled Phase of the study is expected to be approximately 20-21 weeks, including a maximum of 45 days of screening, 11 weeks of double-blind treatment (3-week Titration Period and 8-week Stable Dose Period) and two follow-up TCs for safety, the first 15 (±3) days and the second 30 (+3) days after final dose of study drug for patients who do not participate in the optional OLE Phase of the study.

At the end of 11 weeks of double-blind treatment, eligible patients will be given the opportunity to enter the OLE Phase of the study. The OLE Phase of the study will end at Day 459/Month 15 (Visit 8) for each patient unless the patient withdraws from the study early or the Sponsor elects to terminate the study.

STUDY ASSESSMENTS:

Efficacy Assessments:

Efficacy will be evaluated using the Daytime Sleepiness Scale (DSS), Fatigue Severity Scale (FSS), Cogstate Computerized Cognitive Battery Tests (Identification, Detection, and One Back), Myotonic Dystrophy Health Index (MDHI), ESS, CGI-S, PGI-S, SART, and MWT (for those patients who opt to have this assessment performed).

During the Double-Blind Treatment Phase of the study, patients will undergo efficacy assessments (DSS, FSS, MDHI, ESS, CGI-S, and PGI-S) at Baseline (Visit 2; Day -1), Day 49 (Visit 4), and Day 77 (Visit 5). The optional MWT will be assessed at Baseline (Visit 2, Day -3 to Day -1) and up to

3 days prior to Day 77 (Visit 5); the Cogstate Computerized Cognitive Battery Tests and SART will be performed at Baseline (Visit 2; Day -1) and at Day 77 (Visit 5).

During the OLE Phase, clinical effectiveness will be assessed at all on-site study visits, which occur every 6 months, i.e., on Day 99/Month 3 (Visit 6), Day 279/Month 9 (Visit 7), Day 459/Month 15 (Visit 8/EOT), using DSS, FSS, Cogstate Computerized Cognitive Battery Tests (Identification, Detection, and One Back), MDHI, ESS, CGI-S, and PGI-S.

Safety Assessments:

Safety will be assessed by monitoring and recording of all AEs from signing of the informed consent form (ICF) through the two safety follow-up TCs at 15 (±3) and 30 (+3) days after the final dose of study drug for the Double-Blind Treatment Phase (patients who do not enter the OLE), throughout the OLE Phase of the study by alternating TCs and on-site visits, and through two safety follow-up TCs (which will assess AEs including CV symptoms or psychiatric events and use of concomitant medications) at 15 (±3) and 30 (+3) days after the final dose of open-label pitolisant. Safety assessments also include assessment of suicide risk and suicidality (C-SSRS) during the Double-Blind Phase and OLE Phase of the study.

In addition, 12-lead ECGs (in triplicate) and Holter monitoring will be performed during both the Double-Blind Phase and OLE Phase at time points specified in the Schedule of Assessments for each study phase. The ECG and Holter monitoring performed at Screening will determine whether an exclusionary CV issue is present and testing at later time points during the study is designed to detect any changes in CV parameters. Holter monitoring in the Double-Blind Phase and OLE Phase will be used to test for arrhythmias.

Any QT prolongation or ECG finding deemed clinically significant by the Investigator at any time during the study will be checked against the requirements for discontinuation of study drug (Section 4.4.1) and a follow-up ECG should be scheduled.

A core ECG laboratory will manage all ECG and Holter monitoring activities. All ECGs will be recorded in triplicate. All ECG and Holter data will be transmitted electronically to the core laboratory and will be promptly interpreted by trained cardiologists. Pre-specified ECG criteria for QT, QRS duration, AVB, and arrhythmias will trigger immediate notifications related to ECG and Holter monitoring abnormalities. Any ECG finding that demonstrates QT prolongation (i.e., QTcF >500 msec or an increase of >60 msec regardless of resultant QTc value) should be promptly addressed by the Investigator and will require discontinuation of study drug. In addition to a potential QT prolongation, the Medical Monitor should be consulted for PR >300 msec, QRS >140 msec, or any increase from baseline in PR or QRS greater than 50% or 40%, respectively. The Medical Monitor should also be consulted for any HR increase >65% over baseline or decrease >40% compared with baseline. The ECG should be repeated as soon as possible in the event of these clinically significant results; if done the next day, attempts should be made to perform the repeat ECG at the same time of day that the abnormal ECG was obtained. If the event persists or worsens, study drug will be interrupted for 2-3 days and the ECG will be repeated on the third day. If the abnormality has resolved (i.e., return to baseline values), study drug dosing may resume at the same dose as administered before the interruption (or, in the OLE Phase, resumed with dose adjustment per the Investigator's discretion). If the condition persists or worsens after study drug interruption (or after adjustment in the OLE Phase), treatment with study drug will be permanently discontinued and the subject will be referred to a cardiologist. In addition, in the event of an increase of >60 msec in QTc, study drug will be permanently discontinued, and the subject will be referred to a cardiologist. For all abnormal ECG or Holter monitoring findings considered clinically significant by the Investigator, a follow-up ECG should be performed within 24 hours and again 7 days later to ensure the abnormality is not worsening. These follow-up 12-lead ECGs may be performed locally.

Measurement of laboratory parameters (hematology, serum chemistry, and urine values) and vital signs will be performed at every on-site visit in the Double-Blind Treatment Phase and OLE Phase of the

study. Serum magnesium and potassium values will be monitored at on-site visits in both phases of the study, and patients will be administered supplements if the levels decrease by 20% or if the levels are in the low normal or below normal range. During the Double-Blind Treatment Phase, concomitant medications will be reviewed at every TC and on-site study visit; during the OLE Phase, concomitant medications will be reviewed every 3 months, either by phone call or at on-site study visits. During the OLE Phase, patients will be instructed to avoid strong metabolic inhibitors of CYP2D6 enzymes and strong inducers of CYP3A4 enzymes. If a patient begins taking a strong CYP2D6 inhibitor during the OLE Phase, the pitolisant dose is to be reduced by half. If a patient begins taking a strong CYP3A4 inducer during the OLE Phase, assess for loss of efficacy of pitolisant and for patients stable on pitolisant 8.9 mg or 17.8 mg once daily, increase the dose of pitolisant to double the original daily dose (i.e., 17.8 mg or 35.6 mg, respectively) over 7 days.

Full physical examinations will be performed at Screening and on Day 77 (Visit 5) in the Double-Blind Treatment Phase, and at every on-site visit during the OLE Phase.

At the end of the Double-Blind Treatment Phase (Day 77/Visit 5), patients who do not enter the optional OLE Phase of the study will have two safety follow-up TCs from the study site to assess for AEs (including any CV symptoms and psychiatric events) and use of concomitant medications 15 (±3) days and 30 (+3) days after their final dose of blinded study drug. Patients in the OLE Phase will also have two safety follow-up TCs to assess for AEs (including any CV symptoms and psychiatric events) and use of concomitant medications 15 (±3) days and 30 (+3) days after the final dose of open-label treatment.

Pharmacokinetic Assessments:

During the Double-Blind Treatment Phase, blood samples will be collected to measure concentrations of pitolisant (and its major metabolite) on Day 22 (Visit 3) and Day 77 (Visit 5; end of blinded treatment) for trough and at the time of maximum concentration (t_{max} [3 hours ±30 minutes post dose]). Patients will be instructed to not take their dose of study drug in the morning upon wakening on the days of scheduled study visits that include PK sampling.

Day 22 (Visit 3): At the study site, 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses are to be performed before study drug is administered and at 3 hours (±30 minutes) after dosing. These ECGs must be performed prior to and within 15 minutes of the blood sample being collected for PK analysis. The time of study drug administration and the time of ECGs and blood sample collection for PK must be recorded.

Day 77 (Visit 5): At the study site, 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses are to be performed before study drug is administered and at 3 hours (±30 minutes) after dosing. These ECGs must be performed prior to and within 15 minutes of the blood sample being collected for PK analysis. The time of study drug administration and the time of ECGs and blood sample collection for PK must be recorded.

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

STUDY ENDPOINTS:

Efficacy Endpoints:

Primary efficacy endpoint:

- The primary efficacy endpoint is the change in DSS score from Baseline to Week 11 for pitolisant compared with placebo.

Secondary efficacy endpoints are change from Baseline to Week 11 for pitolisant compared with placebo:

- on the FSS

- in psychomotor function as measured by the Cogstate Detection Test
- in attention as measured by the Cogstate Identification Test
- in working memory as measured by the Cogstate One Back Test
- on the MDHI
- on the ESS
- on the CGI-S (i.e., global assessment of overall severity of EDS as assessed by the clinician)
- on the PGI-S, anchored to EDS
- in attention as measured by SART

Exploratory endpoint:

For patients who complete the MWT assessments:

- change in mean sleep latency (MSL) based on the MWT from Baseline to Week 11 for pitolisant compared with placebo

Long-term effectiveness endpoints:

- Changes from Baseline in DSS, FSS, Cogstate Detection Test, Cogstate Identification Test, Cogstate One Back Test, MDHI, ESS, CGI-S of EDS, and PGI-S of EDS during the OLE Phase of the study.

Safety Endpoints:

The incidence of AEs, changes in clinical laboratory test results and vital signs, 12-lead ECG results (in triplicate), Holter monitoring results, C-SSRS assessment, and physical examination findings will be evaluated.

STATISTICAL METHODS:

Determination of Sample Size:

[redacted]

Efficacy Analyses:

Summary statistics (mean, standard deviation [SD], median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the Baseline Visit to Week 11 for each of the treatment groups and for the active groups combined. The change from Baseline will be analyzed with mixed model repeated measures (MMRM). Fixed effects will be included for treatment visit, treatment × visit interaction, baseline value, and wake-promoting agent stratification factor. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs. placebo and the pooled active groups vs placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts.

A similar approach will be utilized for the OLE Phase effectiveness visits. Summary statistics will be reported for measures of effectiveness at each visit where it is collected.

Safety Analyses:

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

Pharmacokinetic Analyses: Concentrations of pitolisant and its major metabolite will be assayed using a validated bioanalytical method and the concentrations will be reported in the clinical study report (CSR). Concentration-time data of pitolisant and BP1.3484 will be summarized using descriptive statistics.

Interim Analysis: No interim analysis is planned.

SCHEDULE OF ASSESSMENTS, DOUBLE-BLIND TREATMENT PHASE

Visit/TC Study Day	Screening VISIT 1 Day -45 to -2	Baseline VISIT 2 Day -3 to Day -1	Double-Blind Treatment Phase (11 Weeks)							Safety F-Up TC[f]	Unsch Visits[g]
			Titration Period[a] Weeks 1 to 3 Day 1 to 21			Stable Dose Period[b] Weeks 4 to 11 Day 22 to 77					
			Day 1	TC 1 Day 8 (±3 days)	TC 2 Day 15 (±3 days)	VISIT 3 Day 22 (±3 days)	TC 3[c] Day 28 (±3 days)	VISIT 4 Day 49 (±3 days)	EOT[d]/ET[e] VISIT 5 Day 77 (±3 days)		
Informed consent	X										
Assess/confirm eligibility	X	X							X[d]		
Demographics	X										
Medical history	X	X									
Pregnancy test (FCBP)[h]	X	X				X		X	X		
Urine drug screen	X	X							X		
Physical examination[i]	X	X				X		X	X		
Body weight	X	X							X		
Height	X										
Vital signs[j]	X	X				X		X	X		
Clinical laboratory tests	X	X				X		X	X		
Genetic testing for DM1[k]	X										
Holter monitoring[l]	X					X					
12-lead ECG (in triplicate)[m]	X	X				X		X	X		
C-SSRS	X	X		X	X	X	X	X	X		
Blood sample for PK						X[n]			X[o]		
Adverse events[p]	X	X		X	X	X	X	X	X	X	X
Concomitant medication	X	X		X	X	X	X	X	X	X	X

Visit/TC Study Day	Screening VISIT 1 Day -45 to -2	Baseline VISIT 2 Day -3 to Day -1	Double-Blind Treatment Phase (11 Weeks)							Safety F-Up TC[f]	Unsch Visits[g]
			Titration Period[a] Weeks 1 to 3 Day 1 to 21			Stable Dose Period[b] Weeks 4 to 11 Day 22 to 77					
			Day 1	TC 1 Day 8 (±3 days)	TC 2 Day 15 (±3 days)	VISIT 3 Day 22 (±3 days)	TC 3[c] Day 28 (±3 days)	VISIT 4 Day 49 (±3 days)	EOT[d]/ET[e] VISIT 5 Day 77 (±3 days)		
Dispense sleep diary[q]	X										
Randomization		X[r]									
Dispense study drug		X[r]				X		X	X[s]		
Dispense study drug dosing diary[t]		X[r]									
Administer/Titrate Study drug[u]			X[a]	X	X	X	X	X	X		
Study drug compliance/accountability				X	X	X	X	X	X		X
MWT (optional)[v]		X							X		
DSS		X						X	X		
FSS		X						X	X		
Cogstate Detection	X[w]	X							X		
Cogstate Identification	X[w]	X							X		
Cogstate One Back	X[w]	X							X		
MDHI	X	X						X	X		
ESS		X						X	X		
CGI-S	X[x]	X						X	X		
PGI-S		X						X	X		
SART	X[y]	X							X		

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DM1 = myotonic dystrophy Type 1; DSS = Daytime Sleepiness Scale; ECG = electrocardiogram; EOT = end-of-treatment; ESS = Epworth Sleepiness Scale; ET = early termination; FCBP = female of childbearing potential; FSS = Fatigue Severity Scale; F-Up = follow-up; MDHI = Myotonic Dystrophy Health Index; MWT = Maintenance of Wakefulness Test; OLE = Open-Label

Extension; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; SART = Sustained Attention to Response Task; TC = telephone contact; Unsch = unscheduled.

[a] The 3-week Titration Period for the Double-Blind Treatment Phase will be from Day 1 to Day 21 (± 3 days); eligible patients will receive their first dose of study drug on Day 1, and study drug dose will be titrated on Days 8 and 15; all patients will be at their randomized dose of study drug by Day 15. Patients will receive TCs on Day 8 ±3 days (TC 1) and Day 15 ±3 days (TC 2) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, and other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug.

[b] The 8-week Stable Dose Period for the Double-Blind Treatment Phase will be from Days 22 to 77 (±3 days); patients will take their last dose of blinded treatment on Day 77 (±3 days; Visit 5) at the study site; study drug compliance will be monitored by TC and at study visits as detailed in Section 5.5. The EOT (Week 11) optional MWT assessment should not be performed on the same day as the Visit 5 PK as patients will take their dose of study drug at the site after ECGs and pre-dose PK blood draw are done. The EOT (Week 11) optional MWT may be conducted up to 3 days in advance of Day 77; patients should take their dose of study drug on the morning of the scheduled Week 11 MWT assessment.

[c] Patients will receive a TC from study site personnel on Day 28 (±3 days; TC 3) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and review/confirm study drug compliance.

[d] Visit 5 (Day 77 ±3 days) is the EOT Visit for the Double-Blind Treatment Phase. Eligible patients who enter the optional OLE Phase will be dispensed OLE study drug for titration at this visit on Day 77 (Section 5.4.2); eligibility criteria must be confirmed by reviewing the original eligibility criteria in Section 4.1.1 and Section 4.1.2 before a patient can participate in the OLE Phase.

[e] Patients who prematurely discontinue study drug are required to undergo the ET Visit and all ET assessments (Section 7.2.5). Reasons for discontinuation must be recorded.

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

[g] Unscheduled visits and assessments may be conducted by telephone or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator (Section 7.5).

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

[i] Full physical examination is to be performed at the Screening Visit and Visit 5; an abbreviated physical examination is to be performed at Visits 2, 3 and 4 (Section 6.3.2).

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

[k] Genetic testing will be provided by the Sponsor. The results from the genetic test done at Screening should be used for determination of eligibility.

[l] A 24-hour Holter monitor will be placed at the Screening Visit and at Visit 3. A clinically significant finding from Holter monitoring requires additional evaluation (including an unscheduled ECG). On days when a Holter monitor is required (Screening Visit and Visit 3), it should be placed on the patient and the continuous recording started as the 12-lead ECG (in triplicate) data are taken from the Holter monitor recording.

[m] All 12-lead ECGs are to be performed in triplicate. Perform ECGs after the patient has been resting for at least 5 minutes. At Visits 2, 3, and 5, 12-lead ECGs are to be performed before study drug administration. Any clinically significant ECG value is to be promptly addressed by the Investigator in accordance with the protocol.

[n] Patients will be instructed to record in their study diary the time of day that they take the study drug on the day before Visit 3. Patients will be instructed to **not** take their dose of study drug in the morning of Visit 3 (Day 22 ±3 days). Study drug administration will be at the study site and timing will be based on timing of the PK sampling schedule. The Holter monitor should be placed on the patient at the start of the day for Visit 3 and continuous recording started as the 12-lead ECG (in triplicate) data are taken from the Holter monitor recording. At the study site, 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses are to be performed **before** study drug is administered. The 12-lead ECGs should be done prior to and within 15 minutes of the pre-dose blood sample collection for PK analyses. The time of study drug administration and the time of ECG and blood sample collection for PK must be recorded. In addition, 12-lead ECGs and additional PK samples are to be collected at 3 hours (±30 minutes) **after** dosing. Similarly, the 12-lead ECG should be done prior to and within 15 minutes of the post-dose blood sample collection for PK analyses. The time of study drug administration and the time of ECG and blood sample collection for PK must be recorded. The total volume of blood collected is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period.

[o] Patients will be instructed to record in their study diary the time of day that they take study drug on the day before Visit 5. Patients will be instructed to **not** take their dose of study drug in the morning of Visit 5 (Day 77 ±3 days). Study drug administration will be at the study site and timing will be based on timing of the PK sampling schedule. At the study site, 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses are to be performed **before** study drug is administered. The 12-lead ECGs should be done prior to and within 15 minutes of the pre-dose blood sample collection for PK analyses. The time of study drug administration and the time of ECG and blood sample collection for PK must be recorded. In addition, 12-lead ECGs and additional PK samples are to be collected at 3 hours (± 30 minutes) **after** dosing. Similarly, the 12-lead ECG should be done prior to and within 15 minutes of the post-dose blood sample collection for PK analyses. The time of study drug administration and the time of ECG and blood sample collection for PK must be recorded. The total volume of blood collected is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period.

[p] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 days (+3 days) after final dose of study drug (Study Follow-up TCs, Section 7.4). At the Safety Follow-up TCs, AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded.

[q] Patients will be instructed to record what time they went to bed and what time they woke up in the sleep diary during Screening. Eligible patients must have an average of at least 6 hours of sleep per night for at least 7 of 10 consecutive nights including 2 nights that fall on a weekend during Screening. The average should be taken from all days recorded in the patient's sleep diary.

[r] Randomization and dispensing of study drug and study diary will occur after all patient eligibility assessments are conducted, and patient is verified for enrollment.

[s] Eligible patients who enter the OLE Phase will be dispensed OLE pitolisant for titration at Visit 5 (Day 77 ±3 days) and will be instructed to take their first dose of open-label pitolisant on the following day (Day 78 ±3 days).

[t] Patients will be dispensed a study drug dosing diary at the Baseline Visit and will record the number of tablets administered daily (the study drug dosing diary will be used during the Double-Blind Treatment Phase of the study only).

[u] Eligible patients will be instructed to take study drug once daily in the morning upon wakening starting the day after the Baseline Visit (Day 1); exceptions are on the mornings of Visits 3 and 5 when study drug administration will be at the study site (the timing of administration is based on the PK sampling schedule at these visits).

[v] For patients enrolling after protocol Amendment 4 was implemented, the MWT is an optional assessment to be conducted only for those patients who provide written informed consent. These patients must return to the study site on the day before each scheduled MWT assessment (i.e., the day before the MWT Baseline Visit and the day before the EOT MWT assessment in the Double-Blind Treatment Phase [Visit 5]). The MWT baseline assessment may be performed up to 3 days prior to Day 1 to accommodate sleep laboratory scheduling and patient availability. If a patient enrolled prior to protocol Amendment 4 (i.e., had the MWT Baseline assessment) the MWT at Week 11 must be performed. For EOT (Week 11), patients should take their dose of study drug on the morning of the MWT assessment. The MWT should not be performed on the same day as the Visit 5 PK since patients will take their dose of study drug at the site after ECGs and the pre-dose PK blood draw are done.

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

[x] The CGI-S at Screening is required to confirm eligibility for the study.

[y] To familiarize patients with the SART, the test will be administered during Screening.

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

SCHEDULE OF ASSESSMENTS, OPEN-LABEL EXTENSION PHASE

	3-Week Titration Period[a] Day 78 to 98			OLE Long-Term Dosing Period[b] Day 99 to End of Study					
	Week 12	Week 13	Week 14	Week 15	Months 6 and 12	Month 9			
Visit/TC Study Day	**Day 78[c] (±3 days)**	**TC 4 Day 85 (±3 days)**	**TC 5 Day 92 (±3 days)**	**VISIT 6 Day 99 (±3 days)**	**Telephone Contacts[d] Days 189 (Month 6/TC 6), 369 (Month 12/TC 7) (±7 days)**	**VISIT 7 Day 279/Month 9 (±7 days)**	**VISIT 8/ EOT (Day 459/ Month 15)/ ET Visit[e] (±7 days)**	**Safety F-Up[f] TC**	**Unsch visits[g]**
Urine pregnancy test (FCBP)				X		X	X		
Urine drug screen				X		X			
Full physical examination				X		X	X		
Body weight				X		X	X		
Clinical laboratory tests				X		X	X		
Vital signs[h]				X		X	X		
12-lead ECG (in triplicate)[i]				X		X	X		
Holter monitoring[j]				X					
C-SSRS		X	X	X	X	X	X		
Dispense/confirm receipt of study drug[k]				X	X	X			
Administer/Titrate study drug[l]	X[a]	← X[b] →							
Study drug compliance/accountability		X	X	X	X	X	X		X
Concomitant medication		X	X	X	X	X	X	X	X
Adverse events[m]		X	X	X	X	X	X	X	X
DSS				X		X	X		
FSS				X		X	X		

	3-Week Titration Period[a] Day 78 to 98			OLE Long-Term Dosing Period[b] Day 99 to End of Study					
	Week 12	Week 13	Week 14	Week 15	Months 6 and 12	Month 9			
Visit/TC Study Day	**Day 78[c] (±3 days)**	**TC 4 Day 85 (±3 days)**	**TC 5 Day 92 (±3 days)**	**VISIT 6 Day 99 (±3 days)**	**Telephone Contacts[d] Days 189 (Month 6/TC 6), 369 (Month 12/TC 7) (±7 days)**	**VISIT 7 Day 279/Month 9 (±7 days)**	**VISIT 8/ EOT (Day 459/ Month 15)/ ET Visit[e] (±7 days)**	**Safety F-Up[f] TC**	**Unsch visits[g]**
Cogstate Detection				X		X	X		
Cogstate Identification				X		X	X		
Cogstate One Back				X		X	X		
MDHI				X		X	X		
ESS				X		X	X		
CGI-S				X		X	X		
PGI-S				X		X	X		

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DM1 = myotonic dystrophy type 1; DSS = Daytime Sleepiness Scale; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ESS = Epworth Sleepiness Scale; ET = early termination; FCBP = female of childbearing potential; FSS = Fatigue Severity Scale; F-Up = follow-up; MDHI = myotonic dystrophy health index; OLE = open-label extension; PGI-S = Patient Global Impression of Severity; TC = telephone contact; Unsch = unscheduled.

[a] Eligible patients who enter the OLE Phase will begin a 3-week titration period after completion of the Double-Blind Treatment Phase of the study. The Titration Period for the OLE Phase will start on Day 78 (±3 days), i.e., the day after the EOT Visit in the Double-Blind Treatment Phase (Visit 5; Day 77 ±3 days) and will end on Day 98 (±3 days). All patients in the OLE Phase will receive open-label pitolisant and will be titrated to a dose of 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability). The first day of open-label treatment is on Day 78 (±3 days); pitolisant dose will be titrated on Day 85 (±3 days) and again on Day 92 (±3 days). Patients will receive TCs on Days 85 and 92 (±3 days) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and to review/confirm titration of pitolisant dose.

[b] At the end of the 3-week OLE Titration Period, patients will continue to take open-label pitolisant once daily in the morning upon wakening through the EOS (Long-Term Dosing Period). Adjustments to pitolisant dose are permitted as detailed in Section 3.1.2.2. The Open-Label Treatment Period for the OLE Phase will be from Day 99 (±3 days) until Day459/Month 15 (Visit 8; EOT) unless the patient withdraws from the study early or the Sponsor elects to terminate the study.

[c] Day 78 (±3 days) is the first day of open-label pitolisant treatment; there is no visit or TC required on this day. Eligibility will be confirmed on Day 77/EOT Visit 5 in the Double-Blind Treatment Phase.

[d] TCs will be to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, confirm the current dose of study drug and compliance with dosing, and confirm shipment/receipt of study drug sufficient for 3 months (i.e., 90 days) of once daily administration.

[e] All patients will undergo an EOT Visit. Patients who prematurely discontinue study drug are required to undergo the ET Visit (Section 7.3.2.5). Reasons for discontinuation must be recorded.

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

[g] Unscheduled visits and assessments may be conducted by telephone or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator (Section 7.5).

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

[i] All 12-lead ECGs are to be performed in triplicate. Perform ECGs after the patient has been resting for at least 5 minutes. Any clinically significant ECG value is to be promptly addressed by the Investigator in accordance with the protocol. At Visit 6 (Day 99), the Holter monitor should be placed on the patient and continuous recording started, as the 12-lead ECG (in triplicate) data are taken from the Holter monitor recording.

[j] Patients will have a 24-hour Holter monitor placed at Day 99 (±3 days). A clinically significant Holter monitor value is to be promptly addressed by the Investigator in accordance with the protocol.

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

[l] Eligible patients will take the first dose of open-label pitolisant on Day 78 (+3 days) and will be instructed to take study drug once daily in the morning upon wakening.

[m] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 days (+3 days) after final dose of open-label pitolisant (Safety Follow-up TCs, Section 7.4). At the Safety Follow-up TCs, AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded.

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AF	Atrial fibrillation
APC	Atrial premature complex
ASP	Average sleep propensity
AVB	Atrioventricular block
BiPAP	Bilevel Positive Airway Pressure
bpm	Beats per minute
CGI-S	Clinical Global Impression of Severity
cGCP	Current Good Clinical Practice
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical study report
CTG	Cytosine-thymine-guanine
CUG	Cytosine-uracil-guanine
CV	Cardiovascular
CYP	Cytochrome P450
DM	Myotonic dystrophy
DM1	Myotonic dystrophy type 1
DMC	Data Monitoring Committee
DMPK	Dystrophia myotonica protein kinase
DNA	Deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSS	Daytime Sleepiness Scale
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

EDS	Excessive daytime sleepiness
eGFR	Estimated glomerular filtration rate
EOT	End-of-Treatment
ESRD	End-stage renal disease
ESS	Epworth Sleepiness Scale
ET	Early Termination
EU	European Union
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
H_1R	Histamine 1 receptor
H_3R	Histamine 3 receptor
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HST	Home Sleep Test
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IRB	Institutional Review Board
IRT	Interactive response technology
LOE	Lack of effect
LSM	Least square mean
MAR	Missing at random
MDHI	Myotonic Dystrophy Health Index
mITT	Modified intent-to-treat
mRNA	Messenger ribonucleic acid
MSL	Mean sleep latency
MWT	Maintenance of Wakefulness Test
NINDS	National Institute of Neurological Disorders and Stroke

NYHA	New York Heart Association
OLE	Open-Label Extension
PGI-S	Patient Global Impression of Severity
OSA	Obstructive sleep apnea
PK	Pharmacokinetic
PM	Poor metabolizer
PVC	Premature ventricular contraction
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RNA	Ribonucleic acid
RT	Reaction time
SAE	Serious adverse event
SAP	Statistical analysis plan
SART	Sustained Attention to Response Task
SD	Standard deviation
SOP	Standard operating procedure
SOREMP	Sleep-onset rapid eye movement period
TC	Telephone contact
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum concentration
US	United States
USP	United States Pharmacopeia
VT	Ventricular tachycardia

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	**Effective Date**
Protocol Amendment 5	18JUL2023
Protocol Amendment 4	15JUN2022
Protocol Amendment 3, Administrative letter	18JAN2022
Protocol Amendment 3	18NOV2021
Protocol Amendment 2	11AUG2021
Protocol Amendment 1	20MAR2021
Original Protocol	19DEC2020

SUMMARY OF CHANGES, AMENDMENT 5

Table 1 describes the changes made in Amendment 5 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), and in the table of contents, list of abbreviations and definitions of terms, schedules of assessments, references, and synopsis are not listed.

The protocol was primarily amended to revise the anticipated sample size from 78 to 30 patients and to revise the planned statistical analyses.

Table 1: Summary of Changes for Amendment 5

Section Number Section Title	Description of Change	Rationale
Global	Decreased the anticipated sample size from 78 to 30 patients. Removed the Z-score (based on aggregation of the DSS and the MWT scores) as an exploratory endpoint.	Sponsor decision.
	Revised the descriptors of the pitolisant treatment groups from 'low dose' (17.8 mg) and 'high dose' (35.6 mg) to 'lower dose' and 'higher dose', respectively, because both doses are consistent with the FDA-approved prescribing information. Revised the primary efficacy endpoint to indicate that the change in DSS score (not change in mean DSS score) will be the primary efficacy endpoint.	Clarification.
Section 4.2 Method of Assigning Patients to Treatment Groups	Added stratification factor of concomitant use of wake-promoting agents.	Clarification.
Section 9.1.1 Estimand	Revised to indicate the mITT population will be the population used for the efficacy analyses; also retitled Section 9.3.1 to Modified Intent-to-Treat Population.	Clarification.
Section 9.1.2 Multiple Comparisons	Revised to indicate all statistical analyses will be descriptive.	Clarification.
Section 9.1.3 Missing Data	Removed the sensitivity analyses for this exploratory study; also deleted Sensitivity Analyses section (previously Section 9.4.2.1.2).	Sponsor decision.
Section 9.3.5 (removed) MWT Population	Removed the MWT population due to the limited number of patients (≤30 patients) with data for this measure (based on the change made in Amendment 4).	Sponsor decision.

Section Number Section Title	Description of Change	Rationale
Section 9.4.2.1.1 Primary Efficacy Analysis	Revised to indicate that change from Baseline will be analyzed by MMRM, not ANCOVA.	Sponsor decision.
Section 9.4.2.2 Open-Label Extension Analysis	Removed the specification of how the Open-Label Extension Phase data will be summarized.	Sponsor decision.
Section 9.4.4 Pharmacokinetic Analyses	Revised to indicate concentration-time data will be summarized.	Clarification.
Section 12.3 Financial Disclosure	Revised to align with updated protocol template.	Sponsor decision.

ANCOVA = analysis of covariance; DSS = Daytime Sleepiness Scale; FDA = Food and Drug Administration; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures; MWT = Maintenance of Wakefulness Test

SUMMARY OF CHANGES, AMENDMENT 4

Table 2 describes the changes made in Amendment 4 of the protocol. Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.), and in the table of contents, list of abbreviations and definitions of terms, schedules of assessment, and synopsis are not listed.

The protocol was primarily amended to replace the Maintenance of Wakefulness Test (MWT) as the primary endpoint measure with the Daytime Sleepiness Scale (DSS); the MWT assessment was made optional for patients.

Table 2: Summary of Changes for Amendment 4

Section Number Section Title	Description of Change	Rationale
Section 1.2 Rationale for Study Design	[redacted] MWT assessment changed to optional.	Sponsor decision.
Section 2.2 Secondary Objectives	Inserted "selected domains" of cognitive function to reflect that not all domains of cognitive function will be assessed.	Clarification.
Section 3.1.1 Overall Study Design	Updated Figure 1 with the study design changes. Provided instructions for timing of PK, ECG, and MWT procedures.	To align with other changes. Clarification.
Section 3.1.1.1 Screening Period	Specified requirements for recording sleep per night in the sleep diary.	Sponsor decision.
Section 3.1.1.2 Double-Blind Treatment Phase	Updated text to reflect that the MWT assessment is now optional for which patients provide informed consent; provided timing for this assessment.	Clarification based on MWT now being optional.
Section 3.2.1.1.1 Primary Efficacy Endpoint	Replaced MWT with DSS as the primary endpoint measure.	Sponsor decision.
Section 3.2.1.1.2 Secondary Efficacy Endpoints	Removed the DSS and Z-score (based on aggregation of the DSS and the MWT scores) as secondary efficacy endpoints.	Sponsor decision; to align with the endpoint change.
Section 3.2.1.1.3 Exploratory Endpoints	Added new section to designate the MWT and related Z-score endpoints now as exploratory endpoints.	Sponsor decision; to align with the endpoint change.

Section Number **Section Title**	**Description of Change**	**Rationale**
Section 4.1.1 Inclusion Criteria	Inclusion Criterion #2: updated to specify that genetic testing is completed at the Screening Visit. Previous Inclusion Criterion #5: deleted as MWT is no longer required. Inclusion Criterion #5 (previously #6): removed the unnecessary washout period of 14 days.	Clarification. To align with change to MWT. Clarification.
Section 4.1.2 Exclusion Criteria	Exclusion Criterion #1: updated to specify another genetic disorder that is not adequately managed. Exclusion Criterion #2: updated to specify the requirements for recording sleep per night. Exclusion Criterion #6: updated the specified washout period for investigational medication. Exclusion Criterion #8: added that antidepressants that are strong CYP2D6 inhibitors are exclusionary. Exclusion Criterion #12: specified cardiac death as sudden cardiac death. Exclusion Criterion #16: updated to allow patients with 1st degree AVB with an implanted device. Exclusion Criterion #23: added that centrally acting H_1R antagonists are sedating antihistamines; removed the unnecessary washout of one week. Previous Exclusion Criterion #24: deleted redundant criterion regarding medications prolonging the QT interval. Exclusion Criterion #25 (previously #24): updated prohibited use of sleep-promoting agents from one week to one day prior to study-related assessments.	Clarification. Clarification. Clarification. Clarification. Clarification based on KOL and Investigator feedback. Clarification. Clarification. Clarification. Sponsor decision.
Section 4.3 Blinding	Removed text regarding the DMC as there is no longer an interim analysis.	Sponsor decision.
Section 5.7.1 Permitted Concomitant Medications	Added that wake promoting agents prescribed to treat EDS are permitted, and the use of hypnotics is allowed up to 2 nights per week but not the night prior to any efficacy assessment.	Sponsor decision.
Section 5.7.2 Prohibited Medications	Removed the unnecessary reference to a washout of one week; added that centrally acting H_1R antagonists are sedating antihistamines.	Clarifications.
Section 6.2 Efficacy Assessments	Moved the MWT sub-section to the end of the main section as it is now optional.	To align with other changes.

Section Number Section Title	Description of Change	Rationale
Section 6.3.4.1 Holter Monitoring	Added the timing for placing the Holter monitor, and that the ECG is taken from the Holter monitor recording; change made throughout the protocol.	Clarification.
Section 6.3.4.2 12-Lead Electrocardiograms	Specified timing of ECG assessments related to PK blood draws; change made throughout the protocol.	Clarification.
Section 6.3.5 Clinical Laboratory Tests	Added that wake promoting agents prescribed to treat EDS are permitted. Noted in Table 8 additional information regarding a urine drug screen that is positive for amphetamines.	Clarification.
Section 6.5.2 Assessments that may be Completed at the Patient's Home	Added cross reference to Table 10 for other assessments that may be completed at the patient's home.	Clarification.
Section 6.5.3 Other Considerations	Removed MWT as it is no longer the primary endpoint measure, and the assessment is now optional.	To align with previous changes.
Section 7.2.1 Baseline Visit (Visit 2; Day -3 to Day -1)	Removed requirement to complete the MWT as it is now optional and not part of the eligibility criteria. Added information regarding the optional MWT. Updated timing of patient receipt of study drug.	To align with previous changes. Clarification.
Section 7.2.4.1 Visit 3 (Day 22 ±3 Days)	Specified the timing for placement of the Holter monitor, collection of ECG data, and collection of blood for PK analyses. Updated text for patients' receipt of study drug.	Clarification. Clarification.
Section 7.2.4.3 Visit 4 (Day 49 ±3 Days)	Updated text for patients' receipt of study drug.	Clarification.
Section 7.2.4.4 Visit 5 (Day 77 ±3 Days); End-of-Treatment in the Double-Blind Treatment Phase	Specified the timing for collection of ECG data relative to collection of blood for PK analyses. Added information regarding the optional MWT. Removed requirement for Holter monitoring for entering the OLE Phase of the study.	Clarification. To align with previous changes. Sponsor decision.
Section 7.2.5 Early Termination Visit for Double-Blind Treatment Phase	Specified that patients who discontinue from the Double-Blind Treatment Phase of the study prior to Day 77 may not enroll in the OLE Phase of the study.	Sponsor decision.
Section 9.1.1 Estimand	Specified the change in primary endpoint measure from MWT to DSS.	Sponsor decision.

Section Number Section Title	Description of Change	Rationale
	Specified a treatment policy strategy will be utilized to address intercurrent events, with data analyzed as reported.	
Section 9.1.2 Multiple Comparisons	Specified DSS as the primary endpoint measure and how p-values will be reported for secondary and exploratory endpoints.	To align with change to the primary endpoint measure.
Section 9.1.3 Missing Data	Added text related to the primary analysis and for a sensitivity analysis utilizing an MI approach.	Sponsor decision related to the statistical approach.
Section 9.2 Determination of Sample Size	Specified details related to the change in sample size.	To align with change to the primary endpoint measure.
Section 9.3.5 MWT Population	Added section to define the MWT Population as not all patients will complete MWT assessments.	To align with the decision to change the MWT assessment to optional and an exploratory endpoint.
Section 9.4.2.1.1 Primary Efficacy Analysis	Removed text related to the blinded interim analysis.	Sponsor decision.
Section 9.4.2.1.2 Sensitivity Analyses	Specified four instead of three sensitivity analyses (added an ANCOVA model for data imputed using MI).	Sponsor decision related to the statistical approach.
Section 9.4.2.1.2 Secondary Efficacy Analysis	Removed text related to an interim analysis.	Sponsor decision.
Section 9.5 Interim Analysis	Removed text related to an interim analysis.	Sponsor decision.
Appendix E	Updated the list of prohibited medications and added centrally acting to the H_1R antagonist medication type.	To provide additional information and clarity.

ANCOVA = analysis of covariance; AVB = atrioventricular block; CYP = cytochrome P450; DMC = Data Monitoring Committee; DSS = Daytime Sleepiness Scale; ECG = electrocardiogram; EDS = excessive daytime sleepiness; H_1R = histamine 1 receptor; MI = multiple imputation; MWT = Maintenance of Wakefulness Test; OLE = open-label extension; PK = pharmacokinetic

SUMMARY OF CHANGES, AMENDMENT 3 (ADMINISTRATIVE CHANGE)

Minor updates regarding timing of Holter monitoring at Visit 3 (Section 7.2.4.1) and removing reference to Holter monitoring at Visit 5 (Section 7.2.4.4) were made as an administrative

change to the protocol and were sent to Investigators in a letter dated 18 January 2022. These updates were for clarity and accuracy and have been incorporated in protocol Amendment 4.

SUMMARY OF CHANGES, AMENDMENT 3

Table 3 describes the changes made in Amendment 3 of the protocol (dated 18 November 2021). Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.) in the table of contents, list of abbreviations and definitions of terms, and synopsis are not listed.

The protocol was amended primarily to update the eligibility criterion for excessive daytime sleepiness (EDS); specifically, assessment via the Epworth Sleepiness Scale (ESS) was replaced with assessment via the CGI-S for EDS.

Table 3: Summary of Changes for Amendment 3

Section Number Section Title	Description of Change	Rationale
Section 1.2 Rationale for Study Design	Added DSS as an assessment for evaluating sleepiness.	Expert and Investigator feedback; Sponsor decision.
Section 3.1.1.1 Screening Period	Specified that the 7 nights recorded in the sleep diary need to be consecutive nights. Removed reference to determination of AHI/RDI.	Clarification. No longer required per Investigator feedback and Sponsor decision.
Section 3.1.1.2 Double-Blind Treatment Phase	Removed reference to ESS at Baseline as a requirement to confirm eligibility for the study.	To align with the change to eligibility criterion related to EDS.
Section 3.2.1.1.2 Secondary Efficacy Endpoints	Added DSS as first in the list of secondary endpoints and moved ESS to below the MDHI. Replaced ESS with DSS in the z-score.	Expert and Investigator feedback; Sponsor decision. To align with adding the DSS.
Section 3.2.1.2 Long-Term Effectiveness Endpoints	Moved the ESS assessment to be listed after the MDHI assessment.	For consistency with the double-blind phase of the study.
Section 4.1.1 Inclusion Criteria	Updated the eligibility criterion for EDS from assessment via ESS to assessment via CGI-S.	Investigator feedback related to ESS for this patient population; Sponsor decision to replace with CGI-S.
Section 4.1.2 Exclusion Criteria	Exclusion Criterion #2: Specified that the minimum of 7 nights recorded in the sleep diary need to be consecutive nights. Exclusion Criterion #9: Combined with exclusion criterion #10 and removed requirement for determination of AHI/RDI. Exclusion Criterion #17: Removed second reference to non-sustained VT.	Clarification. Investigator feedback and Sponsor decision to streamline criteria related to underlying sleep disorders. Corrected redundancy.

Section Number Section Title	Description of Change	Rationale
Section 6.2 Efficacy Assessments	Added DSS with a description of the instrument (now Section 6.2.1). Reordered ESS to Section 6.2.5.	Expert and Investigator feedback; Sponsor decision. For consistency.
Section 6.2.5 Epworth Sleepiness Scale	Removed reference to the ESS being a self-administered assessment.	Investigator feedback.
Section 6.5.3 Other Considerations Table 10	Added DSS to the list of assessments in Table 10 (Alternate Methods for Completing Study Assessments).	For consistency.
Section 7.1 Screening (Visit 1)	Removed the ESS from Screening. Added the CGI-S assessment as an evaluation done at Screening. Removed reference to determination of AHI/RDI.	Expert and Investigator feedback. To align with the change to eligibility criterion for EDS. To align with the change to exclusion criteria #9 and #10.
Section 7.2 Double-Blind Treatment Phase (Day -1 to Day 77) Section 7.3 Open-Label Extension Phase (Day 78 to End-of-Treatment)	Added DSS as the first efficacy assessment following MWT and moved ESS to occur after the MDHI for all on-site study visits (visits 4-7).	Expert and Investigator feedback; Sponsor decision.
Section 7.2.1 Baseline Visit (Visit 2; Day -1 ± 2 Days)	Removed reference to ESS at Baseline as a requirement to confirm eligibility for the study.	To align with the change to eligibility criterion related to EDS.
Section 8.4.1 Reporting Serious Adverse Events to the Sponsor	Removed reference to telephone notification for reporting SAEs.	Clarification.
Section 9.1.1 Estimand	[redacted]	[redacted]
Section 9.1.2 Multiple Comparisons	[redacted]	[redacted]
Section 9.1.3 Missing Data	[redacted]	[redacted]
Section 9.4.2.1.1 Primary Efficacy Analysis	[redacted]	[redacted]

Section Number Section Title	Description of Change	Rationale
Section 9.4.2.1.2 Sensitivity Analyses	[redacted]	[redacted]

CGI-S = Clinical Global Impression of Severity; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; DSS = Daytime Sleepiness Scale; MDHI = Myotonic Dystrophy Health Index; MWT = Maintenance of Wakefulness Test; SAE = serious adverse event; VT = ventricular tachycardia

SUMMARY OF CHANGES, AMENDMENT 2

Table 4 describes the changes made in Amendment 2 of the protocol (dated 11 August 2021). Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.) in the table of contents, list of abbreviations and definitions of terms, and synopsis are not listed.

The protocol was amended based on the addition of sites in Canada.

Table 4: Summary of Changes for Amendment 2

Section Number Section Title	Description of Change	Rationale
Section 1.2 Rationale for Study Design	Defined the end of the OLE Phase of the study for enrolled patients as Day 459/Month 15 (Visit 8); change also made throughout the protocol.	Sponsor decision.
Section 3.1.1 Overall Study Design Section 3.1.1.3 Open-Label Extension Phase	Defined the end of the OLE Phase of the study for enrolled patients as Day 459/Month 15 (Visit 8); Updated Figure 1 (Overall Study Design) accordingly; Specified the day/month/visit for EOT.	Sponsor decision; additional details for defining the end of the OLE Phase for patients made for clarity.
Section 3.3 Study Duration	Updated based on defining the end of the OLE Phase for enrolled patients.	Sponsor decision.
Section 4.1 Study Population	Updated approximate number of sites from 16 to 22 and added that the study will include sites in Canada.	Sponsor decision.
Section 4.1.2 Exclusion Criteria	Exclusion Criterion #9: Changed AHI/RDI exclusion from >10 to >15 (which reflects unmanaged OSA).	Investigator feedback.
Section 4.6.1 Study Completion Section 4.6.2 Patient Completion	Defined the end of the OLE Phase of the study for enrolled patients; Defined completion for patients in the OLE Phase of the study.	Sponsor decision; additional details for defining the end of the OLE Phase for patients made for clarity.

Section Number Section Title	Description of Change	Rationale
Section 4.7 Screen Failures	Clarified the requirements for patients who re-screen following screen failure.	Clarification.
Section 6.5 Potential Use of Alternative Methods for Completing Study Assessments	Updated section throughout to allow for specific assessments/procedures to be conducted remotely via telemedicine or at the patient's home, no longer just due to restrictions related to COVID-19.	Investigator feedback and Sponsor decision, to allow for greater flexibility and potentially decrease patient burden related to travel to the study site.
Section 7.3 Open-Label Extension Phase (Day 78 to End-of-Treatment)	Updated throughout section to define the end of the OLE Phase of the study for enrolled patients.	Sponsor decision.
Section 9.1.3 Missing Data Section 9.4.2.1.1 Primary Efficacy Analysis	[redacted]	[redacted]

AHI = apnea hypoxia index; COVID-19 = coronavirus disease 2019; EOT = End-of-Treatment; OLE = open-label extension; OSA = obstructive sleep apnea; RDI = respiratory disturbance index

SUMMARY OF CHANGES, AMENDMENT 1

Table 5 describes the changes made in Amendment 1 of the protocol (dated 20 March 2021). Changes related to punctuation and formatting (i.e., changes in numbering, word order, location, etc.) in the table of contents, list of abbreviations and definitions of terms, and synopsis are not listed.

[redacted]

Table 5: Summary of Changes for Amendment 1

Section Number Section Title	Description of Change	Rationale
Section 3.1.1.1 Screening Period	[redacted]	[redacted]
Section 3.1.1.2 Double-Blind Treatment Phase	Specified that both the Baseline ESS and MWT results are needed to confirm eligibility and the timing for these related to dispensing study drug.	Clarification.
Section 4.1 Study Population	[redacted]	[redacted]

Section Number Section Title	Description of Change	Rationale
Section 4.1.1 Inclusion Criteria	[redacted] Inclusion Criterion #6: Updated to define parameters for patients on wake-promoting treatments that could affect EDS and moved use of sleep-promoting treatments to exclusion criteria. Inclusion Criterion #7: Restated serum potassium and magnesium levels as an exclusion criterion (#23); restated ability to ambulate as an inclusion criterion.	[redacted] Based on investigator feedback. For clarity, based on investigator feedback.
Section 4.1.2 Exclusion Criteria	[redacted] Exclusion Criterion #8: Added exclusion for patients not on a stable dose of their antidepressant(s). Exclusion Criterion #9: Updated AHI and RDI indices to >10 (from >5). Exclusion Criterion #10: Specified that sleep disordered breathing and hypoventilation is exclusionary if unmanaged. Exclusion Criterion #13: Specified family member as a first degree relative. Exclusion Criterion #16: Specified symptomatic arrhythmias as being documented. Exclusion Criterion #20: Added that patients with implanted univentricular pacemakers used prophylactically to prevent bradycardia or heart block are not excluded. Exclusion Criterion #22: Specified criteria for hypokalemia and hypomagnesemia. Exclusion Criterion #23: Restated potassium and magnesium levels as exclusionary, and specified parameters for when outside normal ranges. [redacted]	[redacted] Based on investigator feedback. Based on investigator feedback. Based on investigator feedback. For clarity, based on investigator feedback. For clarity, based on investigator feedback. For clarity, based on investigator feedback. For clarity, based on investigator feedback. For clarity, based on investigator feedback. For clarity. [redacted]

Section Number Section Title	Description of Change	Rationale
	Exclusion Criterion #33: Added reference to unstable or uncontrolled medical conditions as part of the Investigator's judgement for exclusion.	
Section 7.1 Screening (Visit 1)	[redacted]	[redacted]
Section 7.2.1 Baseline Visit (Visit 2; Day -1 ±2 Days)	Specified that both the ESS and MWT scores are required to confirm eligibility for the study; therefore, study drug will be dispensed the day following the MWT.	Clarification.
Section 7.2.4.3 Visit 4 (Day 49 ±3 Days)	[redacted]	[redacted]
Section 9.1.1 Estimand Section 9.1.2 Multiple Comparisons Section 9.1.3 Missing Data Section 9.4.2.1.2 Sensitivity Analyses	[redacted]	[redacted]
Section 9.4.2.1.1 Primary Efficacy Analysis	[redacted]	[redacted]
Section 9.4.2.1.2 Secondary Efficacy Analysis	Provided text for this section, which was inadvertently missing in the original protocol.	Correction.
Section 9.5 Interim Analysis	[redacted]	[redacted]

AHI = apnea hypoxia index; ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression of Severity; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; PGI-S = Patient Global Impression of Severity; RDI = respiratory disturbance index

1. INTRODUCTION

1.1. Background Information and Study Rationale

Myotonic dystrophy type 1 (DM1) is a rare genetic disorder that is inherited in an autosomal dominant manner. The prevalence of DM1 ranges from 2.1 to 14.3 per 100,000 people worldwide (Laberge et al 2013), with approximately 40,000 people in the United States (US) with this disorder. More recently, the prevalence of DM1 in the US has been studied and results suggest that as many as 5 per 10,000 people in the US (140,000-150,000) have the genetic defect for DM1, with about 50% likely to be symptomatic, based on the number of repeats in the gene (i.e., >150), and the others possibly not being diagnosed (Johnson 2020). While often considered as primarily a neuromuscular disorder, DM1 is actually a multisystem disorder (Harper 2001). Hallmark signs of the disorder include myotonia, progressive muscular weakness, muscle atrophy, and smooth muscle involvement, but the disorder is also characterized by a wide variety of systemic clinical features, including cardiovascular (CV) conduction and other defects, gastrointestinal motility issues, sleep-disordered breathing, cataracts, endocrinopathies, and multiple abnormalities of the central nervous system (CNS), including excessive daytime sleepiness (EDS), fatigue and cognitive impairment (Heatwole et al 2012; Wenninger et al 2018; Turner and Hilton-Jones 2010). DM1 is also associated with significant incidence of obstructive sleep apnea (OSA) (Subramony et al 2020); however, despite compliance with the standard treatment of continuous positive airway pressure (CPAP), patients with DM1 often experience residual EDS (Gasa et al 2013; Pepin et al 2009).

Myotonic dystrophy results from sequences of deoxyribonucleic acid (DNA) that are expanded abnormally, due to a repeat instability in a non-coding part of a gene. These genetic changes result in a disruption of the messenger ribonucleic acid (mRNA) metabolism, with the consequent formation of aberrant proteins that interfere with nuclear functions and leads to abnormal transcripts in other genes, thus explaining the multisystemic presentation in patients with DM1 (Tieleman et al 2010). The underlying cause of DM1 is a mutation in the dystrophia myotonica protein kinase (DMPK) gene, which encodes a serine/threonine kinase localized to both muscle and nervous tissue (Brook et al 1992). The gene mutation involves an unstable base triplet (cytosine-thymine-guanine [CTG]n) located in the 3' untranslated region of the DMPK gene on the long arm of chromosome 19. In DM1, transcription of the CTG repeats generates cytosine-uracil-guanine (CUG) expansion ribonucleic acids (RNAs) that accumulate in cell nuclei and cause dysregulation of RNA binding proteins. The consequences of RNA binding protein dysregulation are disruption of alternative splicing, mRNA translation, and mRNA stability (Lee and Cooper 2009). The number of the (CTG)n repeats in the DMPK gene varies in the normal population from 3 to 30 units, but in patients with DM1 it varies from 100 up to 1500 or more units (Perini et al 1999). The number of repeats tends to increase from one generation to the next (termed anticipation) and correlates with symptom severity and age of onset, such that the higher the repeat number the greater the severity of symptoms and the earlier the age of onset (Turner and Hilton-Jones 2014; De Antonio et al 2016; Wenninger et al 2018). Adult-onset DM1 is the most common presentation of the disorder.

Dauvilliers and Laberge (2012) noted that EDS is the most common non-muscular complaint in patients with DM1, and it is viewed by patients as a prominent and debilitating feature of the disorder (Laberge et al 2013). This was further validated in the PRISM-1 study, which reported a

prevalence of 87.9% for impaired sleep or daytime sleepiness in a population of patients with DM1, along with one of the highest average life impact scores reported in these patients (2.25 [standard deviation (SD)=1.31], on a scale of 0-4 where a higher number represents a symptom that has a greater effect on a patient's life), second only to fatigue, which had a score of 2.49 (SD=1.22) (Heatwole et al 2012). In patients with DM1, EDS seems to be largely secondary to a dysfunction of brain/brainstem areas regulating sleep patterns, with lesser contributions from sleep fragmentation, sleep-related respiratory events, or periodic leg movements. Interestingly, daytime sleepiness appears to be dissociated from abnormalities in nocturnal breathing (van der Meché et al 1994); when sleep-disordered breathing was successfully treated in this patient population, the symptom of EDS persisted (Dauvilliers and Laberge 2012).

Cheung et al (2018) have reported that significantly lower nadir oxygen (O_2) saturation was found in patients with DM1 versus controls. Some patients with DM1 have also been observed to have sleep-onset rapid eye movement periods (SOREMPs) that resemble those observed in patients with narcolepsy (Park and Radtke 1995; Yu et al 2011; Bonanni et al 2018).

Hypocretin (also known as orexin), a neuropeptide produced exclusively by neurons in the hypothalamus, is involved in maintaining wakefulness and regulating REM sleep (Teske and Mavanji 2012). Decreased cerebrospinal fluid (CSF) levels of this neuropeptide are observed in patients with narcolepsy and are an underlying cause of that sleep disorder (Nishino et al 2000; Peyron et al 2000; Thannickal et al 2000; Mignot et al 2002). Several studies have reported decreased levels of hypocretin in CSF from patients with DM1, but the results are inconsistent. Martinez-Rodriguez et al (2003) found decreased CSF orexin levels in patients with DM1, while Ciafaloni et al (2008) reported that CSF orexin levels in patients with DM1 were not different from the control group. Omori et al (2018) found that 7 of 17 patients with DM1 and associated EDS showed decreased CSF orexin levels, with significant differences in Epworth Sleepiness Scale (ESS) scores and mean sleep latency (MSL) between patients with DM1 with decreased CSF hypocretin (i.e., ≤200 pg/mL) versus normal controls (i.e., >200 pg/mL).

Excessive daytime sleepiness is a symptom that is common among neurological and neuromuscular disorders, but whether the underlying cause of this symptom is similar across disease states remains unclear. However, evidence suggests that drugs effective in alleviating EDS in one disease state will be effective for this symptom in another disease state.

Psychostimulant drugs (i.e., modafinil and methylphenidate) approved for the treatment of EDS in narcolepsy, which is characterized by a loss of CNS orexin (hypocretin), have been studied in patients with DM1. Modafinil, approved for the treatment of EDS associated with narcolepsy, has been used with equivocal success in patients with DM1 (Damian et al 2001; MacDonald et al 2002; Talbot et al 2003; Wintzen et al 2007; Orlikowski et al 2009; West et al 2016) and, while Puymirat et al (2012) have shown benefit of methylphenidate for EDS in patients with DM1, this observation has not been independently replicated in another double-blind study. Additional well controlled, randomized trials are needed to establish the safety and efficacy of psychostimulants in the treatment regimen for patients with myotonic dystrophy (DM) (Annane et al 2006).

Pitolisant (brand name WAKIX®) was approved in the European Union (EU) in March 2016 for the treatment of adults with narcolepsy with or without cataplexy and has since been approved in the US for the treatment of EDS or cataplexy in adult patients with narcolepsy.

Pitolisant is a first-in-class, potent and highly selective histamine 3 receptor (H_3R) antagonist/inverse agonist with a novel mechanism of action. It triggers long-lasting activation of histaminergic neurons in the brain, a neuronal system involved in the maintenance of wakefulness, attention, and cognition. Pitolisant binds to H_3Rs and blocks the normal negative feedback mechanism for histamine release, resulting in increased release of this wake-promoting neurotransmitter. It also functions as an inverse agonist, resulting in enhanced histamine synthesis and release from presynaptic neurons.

Pitolisant easily crosses the blood-brain barrier so that after low oral doses, it elicits histamine release in the central nervous system. It also increases the release of other wake-promoting neurotransmitters (including dopamine, norepinephrine, serotonin, and acetylcholine) via heteroreceptors within those neuronal systems. Importantly, pitolisant does not increase dopamine release in the striatum, including the nucleus accumbens, which differentiates pitolisant from other wake-promoting agents that have abuse liability, such as psychostimulants.

Pitolisant, unlike psychostimulants, is not a scheduled drug, and thus can potentially offer a better benefit/risk profile in comparison to other potential treatments for EDS associated with DM1. Pitolisant presents a novel approach to the management of EDS in patients with DM1, and based on its mechanism of action, could potentially impact the management of other non-muscular symptoms, including fatigue and cognitive dysfunction. To date, no clinical studies have been conducted to evaluate pitolisant in patients with DM1. This Phase 2 study will evaluate the impact of pitolisant on non-muscular symptoms of DM1 in adults, with a focus on EDS, fatigue, cognitive function, and overall burden of disease.

1.2. Rationale for Study Design

This randomized, double-blind, placebo-controlled study with an optional open-label extension (OLE) will evaluate the safety and efficacy of pitolisant compared with placebo in the treatment of EDS and other non-muscular symptoms (including fatigue, cognitive function, and overall burden of disease) in patients with DM1 ages 18 to 65 years.

In the randomized Double-Blind Treatment Phase, approximately 30 eligible patients ages 18 to 65 years will be enrolled in the study and will be randomized in a 1:1:1 ratio. Investigators and patients will be blinded to treatment assignment, minimizing potential bias in safety and efficacy assessments. The OLE Phase will allow for eligible patients (regardless of their treatment assignment in the Double-Blind Treatment Phase) to receive pitolisant until Day 459/Month 15 (Visit 8) unless the patient withdraws from the study early or the Sponsor elects to terminate the study. The OLE will also allow for the assessment of long-term safety and effectiveness of pitolisant in this patient population.

The primary efficacy endpoint in the study is the change in mean Daytime Sleepiness Scale (DSS) score from Baseline to Week 11 for pitolisant compared with placebo. A description of the DSS is provided in Section 6.2.1. Secondary efficacy endpoints will be evaluated using validated scales and measures. Change in sleepiness, fatigue, cognitive symptoms of DM1, and the overall burden of disease from the patient's perspective will be evaluated using the DSS and ESS, the Fatigue Severity Scale (FSS), the Cogstate Computerized Cognitive Battery Tests and Sustained Attention to Response Task (SART), and the Myotonic Dystrophy Health Index (MDHI). Secondary efficacy endpoints of clinician-rated impression of the severity of the patient's EDS and patient-rated impression of the severity of their EDS will be evaluated using

the global impression scales of Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Severity (PGI-S), respectively. Descriptions of the scales and measures used to evaluate the secondary endpoints are provided in Section 6.2.

Patients with DM1 have an increased CV liability and risk of sudden death (Groh 2012). Cardiac manifestations of the disease present most commonly as arrhythmias or conduction disturbances (Lau et al 2015). Approximately 65% of patients have electrocardiogram (ECG) abnormalities, and specific ECG abnormalities have been noted as a sensitive predictor of sudden death, and thus may be useful for risk stratification in this population (Lau et al 2015; Sommerville et al 2017). Specifically, risk of sudden death is significantly elevated in patients whose ECG shows atrial arrhythmia, PR interval >240 msec, QRS duration >120 msec, or advanced atrioventricular block (AVB) (Groh 2012). Therefore, in this Phase 2 study, the exclusion criteria will ensure the enrollment of patients with minimal conduction defects and low risk for clinically significant cardiac arrhythmias. Because pitolisant has the potential for QT prolongation, patients with potential for QT prolongation are excluded, as are patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers (PMs) (pitolisant exposure is 2- to 3-fold higher in CYP2D6 PMs). In addition, patients' CV status will be monitored clinically throughout the study using triplicate ECG assessments and Holter monitoring. This additional monitoring is warranted because up to 32% of patients with DM1 with a normal ECG may have arrhythmias and conduction abnormalities that are only detectable using arrhythmia monitoring (Merlevede et al 2002).

1.3. Dose Rationale

Eligible patients (approximately 30 in total) will be randomized at a 1:1:1 ratio to one of three treatment groups: higher dose pitolisant, lower dose pitolisant, or placebo. The proposed lower and higher doses of pitolisant for the Double-Blind Treatment Phase of the study are 17.8 mg and 35.6 mg, respectively, administered once daily in the morning upon wakening for 8 weeks following a 3-week titration period. In the OLE Phase, all patients will receive open-label pitolisant and will be titrated to a dose of 35.6 mg, or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability. The pitolisant doses are the same as those that are approved by the Food and Drug Administration (FDA) for the narcolepsy indication. Dosing in both the Double-Blind Treatment Phase and OLE Phase of the study will include a 3-week titration period, which is consistent with the FDA-approved prescribing information for WAKIX® (pitolisant).

1.4. Potential Risks and Benefits

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

(N=1513) were headache (13.5%), insomnia (8.5%), and nausea (5.8%); the majority of these events were considered treatment related.

Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment. Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant is not recommended in patients with end-stage renal disease (ESRD).

Pitolisant prolongs the QT interval. The use of pitolisant should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Pitolisant is contraindicated in patients with severe hepatic impairment and is not recommended in patients with ESRD. To mitigate potential CV risks in this study, patients with potential for QT prolongation and patients who are known CYP2D6 PMs are excluded from participation and CV status of all patients will be monitored throughout the study using triplicate ECGs and Holter monitoring.

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

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of pitolisant compared with placebo in treating EDS in patients with DM1 ages 18 to 65 years.

2.2. Secondary Objectives

The secondary objectives of this study are to assess:

- the impact of pitolisant on fatigue in patients with DM1
- the impact of pitolisant on selected domains of cognitive function in patients with DM1
- investigator and patient impression of overall impact of pitolisant on burden of disease in patients with DM1
- safety and effectiveness of pitolisant during long-term treatment (during the OLE Phase)

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is an exploratory, randomized, double-blind, placebo-controlled, parallel-group study in adult patients (ages 18 to 65 years) with DM1, followed by an optional OLE Phase.

The study will consist of a Screening Period (up to 45 days), an 11-week Double-Blind Treatment Phase (including a 3-week Titration Period and an 8-week Stable Dose Period), and an optional OLE Phase. The OLE Phase will continue until Day 459/Month 15 (Visit 8) for each patient unless the patient withdraws from the study early or the Sponsor elects to terminate the study. An overall schema of the study design is provided in Figure 1.

After Screening, approximately 30 patients ages 18 to 65 years who meet all eligibility criteria will be randomized at the Baseline Visit in a 1:1:1 ratio to lower dose pitolisant (17.8 mg), higher dose pitolisant (35.6 mg), or matching placebo. In the Double-Blind Treatment Phase, patients will be titrated to their randomized stable dose of study drug during the 3-week Titration Period (Table 6). After completion of the 3-week Titration Period, patients will continue to take study drug at their randomized dose once daily in the morning upon wakening for an additional 8 weeks of blinded treatment (Stable Dose Period). The duration of the Double-Blind Treatment Phase will be 11 weeks. Adjustments to study drug dosing outside of the protocol-specified titration schedule are not allowed during the 11-week Double-Blind Treatment Phase.

Following the 11-week Double-Blind Treatment Phase, eligible patients will be given the opportunity to participate in an optional OLE Phase. During the OLE Phase, all eligible patients will receive treatment with open-label pitolisant and will be titrated during a 3-week Titration Period to a dose of 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability) (Table 7). Adjustments to pitolisant dose are permitted during the OLE Phase; pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability; the maximum dose allowed is 35.6 mg once daily.

Safety, efficacy, and PK of pitolisant will be evaluated in the Double-Blind Treatment Phase (Section 3.1.1.2) and safety and effectiveness of pitolisant will be evaluated in the OLE Phase (Section 3.1.1.3).

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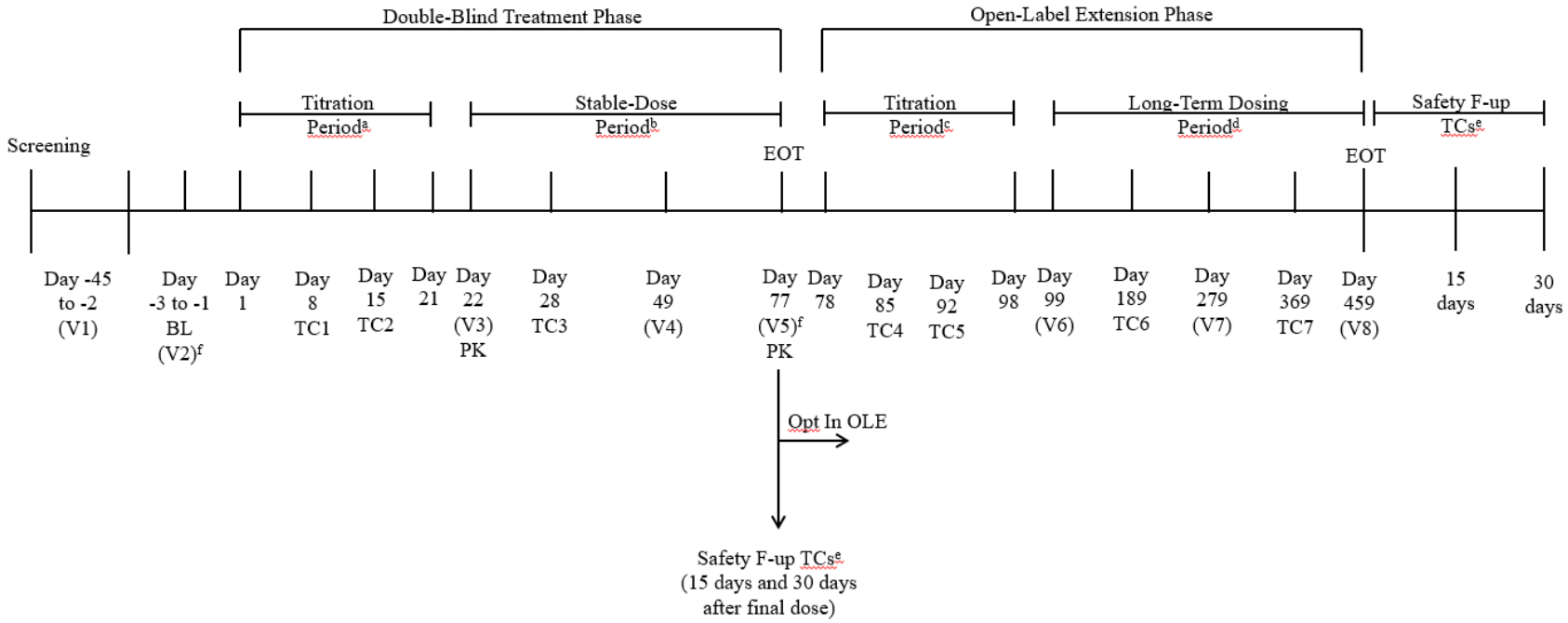
Figure 1: Overall Study Design



Abbreviations: AE = adverse event; BL = baseline; C-SSRS = Columbia-Suicide Severity Rating Scale; EOT = end-of-treatment; F-up = follow-up; MWT = Maintenance of Wakefulness Test; OLE = Open-Label Extension; PK = pharmacokinetics; TC = telephone contact; V = visit.

[a] The Titration Period for the Double-Blind Treatment Phase will be from Days 1 to 21. Patients will receive their first dose of study drug on Day 1; study drug dose will be titrated on Day 8 and again on Day 15 (as appropriate based on randomized dose; Table 6); all patients will be at their final randomized dose by Day 15 of the Titration Period.
[b] The 8-week Stable Dose Period for the Double-Blind Treatment Phase will be from Days 22 to 77 (±3 days); patients will take their last dose of blinded treatment on Day 77 (±3 days). Visit 5 (Day 77 ±3 days) is the EOT Visit for the Double-Blind Treatment Phase. The EOT (Week 11) MWT assessment should not be performed on the same day as the Visit 5 PK as patients will take their dose of study drug at the site after ECGs and the pre-dose PK blood draw are done. The EOT (Week 11) MWT may be conducted up to 3 days in advance of Day 77; patients should take their dose of study drug on the morning of the scheduled Week 11 MWT assessment. Eligible patients who opt to enter the OLE Phase will be dispensed OLE study drug for titration at this visit.
[c] The Titration Period for the OLE Phase will be from Days 78 to 98 (±3 days). Eligible patients will receive their first dose of open-label pitolisant on Day 78 and pitolisant dose will be titrated on Day 85 and again on Day 92 to a dose of 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability). At the end of the 3-week Titration Period, patients will continue to take pitolisant 35.6 mg (or their maximum dose up to 35.6 mg based on Investigator assessment of tolerability) once daily in the morning upon wakening until the end of the study (Long-Term Dosing Period). During the OLE Phase, pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability. The maximum pitolisant dose allowed in the study is 35.6 mg.

[d] In between the 6-monthly on-site study visits, patients will receive a TC from the study site approximately every 180 days (i.e., on Days 189 and 369) to record AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete C-SSRS, confirm the current dose of study drug and compliance with dosing, and confirm shipment/receipt of study drug sufficient for 3 months (i.e., 90 days) of once daily administration.

[e] All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 days (+3 days) after final dose of study drug (Safety Follow-up TCs, Section 7.4). At the Safety Follow-up TCs, AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use will be recorded.

[f] Patients who consent to the optional MWT must return to the study site on the day before the scheduled Baseline MWT assessment and the day before the scheduled EOT MWT assessment of the Double-Blind Treatment Phase.

3.1.1.1. Screening Period

The Screening Period will be a maximum of 45 days. At the Screening Visit (Visit 1), after written informed consent is provided, patients will undergo screening assessments. Screening will include fitting of a 24-hour Holter monitor; a clinically significant finding from Holter monitoring will require additional evaluation including an unscheduled ECG (Section 6.3.4). Patients will be provided with a sleep diary (Appendix A) and will be asked to record their time to bed and time of wakening for at least 7 of 10 consecutive nights including 2 nights that fall on a weekend during Screening. Patients who meet all eligibility criteria will be enrolled in the study.

3.1.1.2. Double-Blind Treatment Phase

At the Baseline Visit (Day -3 to Day -1, Visit 2), after completion of all Baseline assessments, patients who continue to meet all eligibility criteria will be randomized at a 1:1:1 ratio to receive once daily treatment with lower dose pitolisant (17.8 mg), higher dose pitolisant (35.6 mg), or matching placebo in the Double-Blind Treatment Phase. Eligible patients will be dispensed study drug and instructed to take study drug once daily in the morning upon wakening in accordance with the schedule outlined in Table 6. Patients will be instructed to take their first dose of blinded study drug on the morning after they receive study drug from the site. Patients will be provided with a study drug dosing diary at the Baseline Visit and will be instructed to record the number of tablets administered (and from which bottle) daily. The study drug dosing diary will be used in the Double-Blind Treatment Phase only (an example of the study drug dosing diary is provided in Appendix B).

Patients will be titrated during a 3-week Titration Period to their randomized dose of study drug as detailed in Table 6; study drug dose will be titrated on Day 8 and again on Day 15, with all patients at their randomized dose by Day 15. At the end of the 3-week Titration Period, patients will continue to take study drug (blinded pitolisant or placebo) in accordance with their randomized dose once daily in the morning upon wakening for an additional 8 weeks (Stable Dose Period; Days 22 to 77) for a total of 11 weeks of double-blind treatment.

Table 6: Study Drug Dosing in the Double-Blind Treatment Phase

	Titration Period (3 Weeks)			Stable Dose Period (8 Weeks)
Treatment Groups	**Week 1 (Days 1 - 7)**	**Week 2 (Days 8 - 14)**	**Week 3 (Days 15 - 21)**	**Weeks 4 - 11 (Days 22 - 77)**
Lower dose pitolisant	4.45 mg	8.9 mg	17.8 mg	17.8 mg
Higher dose pitolisant	8.9 mg	17.8 mg	35.6 mg	35.6 mg
Placebo	Matching tablets	Matching tablets	Matching tablets	Matching tablets

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

For patients enrolling after protocol Amendment 4 was implemented, the MWT is an optional assessment for which patients provide consent. Patients must return to the study site on the day

before each scheduled MWT assessment (i.e., the day before the MWT Baseline Visit and the day before the EOT MWT assessment of the Double-Blind Treatment Phase [Visit 5]). The MWT Baseline assessment may be performed up to 3 days prior to Day 1 to accommodate sleep laboratory scheduling and patient availability. If a patient enrolled prior to protocol Amendment 4 (i.e., had the MWT Baseline assessment) the MWT at Week 11 must be performed. For EOT (Week 11), patients should take their dose of study drug on the morning of the scheduled MWT assessment. The MWT should not be performed on the same day as the Visit 5 PK as patients will take their dose of study drug at the site after ECGs and the pre-dose PK blood draw are done.

Adjustments to study drug dosing outside of the protocol-specified titration schedule are not permitted during the 11-week Double-Blind Treatment Phase; however, interruptions in study drug dosing may be allowed (e.g., for an adverse event [AE]) as detailed in Section 3.1.3.

Patients will receive telephone contacts (TCs) from the study site on Days 8, 15, and 28 (±3 days) (TCs 1, 2, and 3, respectively) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the Columbia-Suicide Severity Rating Scale (C-SSRS) and review/confirm titration of study drug. During the 8-week Stable Dose Period, patients will undergo safety and efficacy assessments at the study site on Days 22 (Visit 3), 49 (Visit 4), and 77 (Visit 5) (window for Visits 3, 4, and 5 is ±3 days). Blood sampling for PK assessments will be done at Days 22 (Visit 3) and 77 (Visit 5). On Day 22 (Visit 3), safety assessments will include fitting of a Holter monitor; the patient will wear the monitor for 24 hours and the device will be returned to the study site via courier or directly to the site if the patient is able, as detailed in a separate instructional document. A clinically significant finding from Holter monitoring at any time during the study will require additional evaluation including an unscheduled ECG; further details on Holter monitoring at each visit are provided in Section 6.3.4.1.

At the end of the Double-Blind Treatment Phase, eligible patients will be given the opportunity to enter an optional OLE Phase (Section 3.1.1.3). If a patient does not enter the OLE Phase, the patient will receive Safety Follow-up TCs from the study site 15 (±3) days and 30 (+3) days after their final dose of blinded treatment to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and use of concomitant medications (Section 7.4).

3.1.1.3. Open-Label Extension Phase

Before patients can enter the OLE Phase of the study, eligibility criteria must be confirmed at Visit 5 (i.e., the End of Treatment [EOT] Visit in the Double-Blind Treatment Phase).

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

Regardless of the patient's assigned randomization during the Double-Blind Treatment Phase, which will remain blinded at entry into the OLE Phase, all eligible patients who enter the OLE Phase will be titrated during a 3-week Titration Period to a dose of 35.6 mg open-label pitolisant

(or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability), as detailed in Table 7. Eligible patients will be dispensed open-label pitolisant for titration at Visit 5 (Day 77 ±3 days) of the Double-Blind Treatment Phase and will take their first dose of open-label pitolisant the following morning upon wakening (Day 78 ±3 days). Pitolisant dose will be titrated on Day 85 (±3 days) and again on Day 92 (±3 days) (Table 7). At the end of the 3-week OLE Titration Period, patients will continue to take open-label pitolisant 35.6 mg (or their maximum dose up to 35.6 mg based on Investigator assessment of tolerability) once daily in the morning upon wakening through the end of the study (Long-Term Dosing Period).

Adjustments to pitolisant dose are permitted in the OLE Phase; pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability; the maximum dose allowed in the study is 35.6 mg. Details for pitolisant dose adjustments are provided in Section 3.1.2.2.

Table 7: Pitolisant Dosing in the Open-Label Extension Phase

	Titration Period[a] (3 Weeks)			Long-Term Dosing Period[b]
	Week 12 (Days 78 - 84)	**Week 13 (Days 85 - 91)**	**Week 14 (Days 92- 98)**	**Weeks 15 (Day 99) to EOT**
Pitolisant dose	8.9 mg	17.8 mg	35.6 mg	35.6 mg

Abbreviations: EOT = End-of-Treatment; OLE = Open-Label Extension.

[a] Pitolisant dose will be titrated on Day 85 and again on Day 92.
[b] After completion of the 3-week Titration Period, patients will continue to receive pitolisant 35.6 mg (or their maximum dose up to 35.6 mg based on Investigator assessment of tolerability).

Note: Adjustments to study drug dosing after the protocol-specified titration period are permitted during the OLE Treatment Phase of the study, where the pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability; the maximum pitolisant dose allowed in the study is 35.6 mg (Section 3.1.2.2) It is recommended that adjustments made during this time be to one of the three pre-specified doses of 35.6 mg, 17.8 mg, or 8.9 mg. If deemed necessary by the Investigator, alternative doses may be prescribed during the OLE Phase; however, the Investigator must first consult with the Medical Monitor. Dosing may be adjusted in increments of 4.45 mg.

During the OLE Phase, patients will receive TCs from the study site on Days 85 and 92 (±3 days) during the 3-week Titration Period to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and review/confirm pitolisant dose titration. A clinically significant finding from Holter monitoring at any time during the study will require additional evaluation, including an unscheduled ECG (Section 6.3.4).

At the end of the OLE Titration Period, patients will return to the study site for assessment of safety and effectiveness on Day 99 (±3 days; Visit 6); 24-hour Holter monitoring will be initiated at this visit (Section 6.3.4.1). The patient will wear the monitor for 24 hours and the device will be returned to the study site via courier or directly to the site if the patient is able, as detailed in a separate instructional document. A clinically significant finding from Holter monitoring at any time during the study will require additional evaluation, including an unscheduled ECG (Section 6.3.4).

A TC will occur 3 months after Visit 6 on Day 189/Month 6 followed by an on-site study visit (Visit 7) 3 months later (Day 279/Month 9). Another TC will occur 3 months later on Day 369/Month 12. All patients who complete the study will have an EOT visit at Day 459/Month 15 (Visit 8) unless the patient withdraws from the study early or the study is terminated by the Sponsor. A 3-month supply of study drug (i.e., sufficient for 90 days of once daily administration) will be provided to eligible patients every 3 months either via mail or at the on-site study visits; additional study drug may be dispensed between TCs and/or on-site visits if necessary. At all on-site study visits (approximately every 6 months), assessment of safety and effectiveness will be performed. If CV assessments are required at the discretion of the Investigator, patients will return to the study site for unscheduled visits that will include an ECG as detailed in Section 7.5.

All patients will undergo an EOT Visit (Section 7.3.2.4). Patients will receive Safety Follow-up TCs from the study site 15 (±3) days and 30 (+3) days after their final dose of open-label pitolisant to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use (Section 7.4).

3.1.2. Dose Adjustments

3.1.2.1. Double-Blind Treatment Phase

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

3.1.2.2. Open-Label Extension Phase

Adjustments in pitolisant dose are permitted in the OLE Phase. Pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability. Decreases in pitolisant dose are permitted at any time at the discretion of the Investigator. For patients who are on less than the maximum dose of 35.6 mg pitolisant, dose increases are at the Investigator's discretion in consultation with the Medical Monitor. Discussions and decisions regarding adjustments in pitolisant dose will occur over the telephone or during on-site study visits (either scheduled or unscheduled). Pitolisant doses may be adjusted (higher or lower). It is recommended that adjustments made during this time be to one of the three pre-specified doses of 35.6 mg, 17.8 mg, or 8.9 mg. If deemed necessary by the Investigator, alternate doses may be prescribed during the OLE Phase; however, the Investigator must first consult with the Medical Monitor. Dosing may be adjusted in increments of 4.45 mg. The maximum permitted pitolisant dose in the study is 35.6 mg once daily.

In the event a patient has clinically significant abnormal ECG results, study drug may need to be adjusted and/or interrupted as detailed in Section 4.4.2 and Section 6.3.4.2.

In the event a patient develops moderate hepatic impairment (Child-Pugh B) or moderate or severe renal impairment during the OLE Phase of the study, the dose of pitolisant may need to be decreased by the Investigator in consultation with the Medical Monitor; a maximum daily dose of 17.8 mg is recommended in either situation. Patients who develop either ESRD (estimated glomerular filtration rate [eGFR] of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C) must be withdrawn from the study (Section 4.4.1).

If a patient begins taking a strong CYP2D6 inhibitor during the OLE Phase, pitolisant dose is to be reduced by one half (Section 5.7.3). If a patient begins taking a strong CYP3A4 inducer during the OLE Phase, pitolisant dose may be increased up to the maximum permitted daily dose of 35.6 mg; procedures for pitolisant dose increases must be followed, as outlined in this section.

3.1.3. Dose Interruptions

Every effort should be made to educate patients on the importance of remaining compliant with study drug dosing.

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

In the OLE Phase of the study, interruptions in study drug dosing are permitted based on tolerability and the discretion of the Investigator. Additionally, clinically significant ECG results may warrant interruption of study drug dosing as detailed in Section 4.4.2.

If a dose is missed in the OLE Phase, the patient should take the next dose the following morning upon wakening. If a patient is taking a pitolisant dose greater than 8.9 mg and has a dosing interruption exceeding 7 days in the OLE Phase, before restarting study drug, the Investigator should consult with the Medical Monitor and consider re-titrating the patient to the desired dose as detailed in Section 3.1.1.3.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

Efficacy endpoints are to be assessed by comparison of patients treated with pitolisant versus patients who received placebo.

3.2.1.1. Double-Blind Treatment Phase

3.2.1.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in DSS score from Baseline to Week 11 for pitolisant compared with placebo.

3.2.1.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are change from Baseline to Week 11 for pitolisant compared with placebo:

- on the FSS
- in psychomotor function as measured by the Cogstate Detection Test
- in attention as measured by the Cogstate Identification Test
- in working memory as measured by the Cogstate One Back Test
- on the MDHI

- on the ESS
- on the CGI-S (i.e., global assessment of overall severity of EDS as assessed by the clinician)
- on the PGI-S, anchored to EDS
- in attention as measured by SART

3.2.1.1.3. Exploratory Endpoint

For patients who complete the MWT assessments:

- change in MSL based on MWT from Baseline to Week 11 for pitolisant compared with placebo

3.2.1.2. Long-Term Effectiveness Endpoints

Long-term effectiveness endpoints for EDS, fatigue, cognitive function, and overall disease burden will be evaluated as measured by changes from baseline in DSS, FSS, Cogstate Detection Test, Cogstate Identification Test, Cogstate One Back Test, MDHI, ESS, CGI-S of EDS, and PGI-S of EDS during the OLE Phase of the study.

3.2.2. Safety Endpoints

Safety will be assessed by monitoring the incidence of AEs and changes in clinical laboratory test results, vital signs, 12-lead ECG results (in triplicate), Holter monitoring results, C-SSRS assessment, and physical examination findings from Baseline to Week 11 in the Double-Blind Treatment Phase and from Baseline to study completion in the OLE Phase.

3.3. Study Duration

The study is expected to be multi-year in duration. The Double-Blind Treatment Phase will remain open until the last patient completes this phase of the study, and the OLE Phase will remain open until the final patient enrolled reaches their Day 459/Month 15 (Visit 8/EOT) visit or the Sponsor elects to terminate the study.

The duration of participation for individual patients in the Double-Blind Treatment Phase is expected to be up to approximately 21 weeks, including a maximum of 45 days of screening, 11 weeks of double-blind treatment (includes a 3-week Titration Period and 8-week Stable Dose Period) and 30 days of safety follow-up for patients who do not enter the optional OLE Phase of the study. For patients who enter the OLE Phase of the study, individual patient participation is expected to continue until the patient reaches Day 459/Month 15 (Visit 8) and then for an additional 30 days of safety follow-up.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 30 patients with DM1 are planned to be enrolled in the study at approximately 22 sites in the US and Canada.

4.1.1. Inclusion Criteria

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

1. Is able to provide voluntary, written informed consent.
2. Has a diagnosis of DM1 confirmed by genetic testing (CTG repeat of ≥100) from the Screening Visit.
3. Male or female patients ages 18 to 65 years at the time of enrollment.
4. [redacted]
5. If on a wake-promoting treatment that could affect EDS (including stimulants, modafinil, and armodafinil):
    a. Must be on a stable dose for at least 2 months prior to Screening and agree to continue the stable dose for the duration of the Double-Blind Treatment Phase of the study (dose adjustments will be permitted in the OLE Phase).
    b. If not on a stable dose for 2 months prior to Screening, washout for 5 half-lives prior to randomization and agree to remain off these treatments for the duration of the Double-Blind Treatment Phase of the study.
6. Washout of cannabidiol and tetrahydrocannabinol for 28 days prior to randomization and agree to remain off for the duration of the Double-Blind Treatment Phase of the study.
7. Able to walk independently with or without an assistive device (e.g., cane, walker, orthoses allowed).
8. A patient who is a female of child-bearing potential (FCBP) must have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test at the Baseline Visit and agree to remain abstinent or use an effective method of non-hormonal contraception to prevent pregnancy for the duration of the study and for 21 days after final dose of study drug.
9. In the opinion of the Investigator, patient is capable of understanding and complying with the protocol and administration of oral study drug.

4.1.2. Exclusion Criteria

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

1. Has a diagnosis of another genetic or chromosomal disorder that is distinct from DM1 and that is not being managed adequately in the opinion of the Investigator.

2. [redacted]
3. Consistently consumes >600 mg of caffeine per day and is unable/unwilling to reduce caffeine intake to <600 mg per day for the duration of the Double-Blind Treatment Phase of the study; caffeine intake should remain consistent during Screening and throughout the Double-Blind Treatment Phase of the study.
4. Does not agree to discontinue any prohibited medication or substances listed in the protocol.
5. Is currently breastfeeding or planning to breastfeed over the course of the study. Lactating women must agree not to breastfeed for the duration of the study (Double-Blind Treatment Phase and OLE Phase) and for 21 days after final dose of study drug.
6. Participation in an interventional research study involving another investigational medication or device in the 28 days prior to enrollment; patients who undergo a washout of an investigational medication of at least 5 half-lives can be enrolled in the Double-Blind Treatment Phase of the study. Patients considering participation in another interventional research study in the OLE Phase must consult with the Investigator who will consult with the Medical Monitor.
7. Has a primary diagnosis of severe psychiatric illness.
8. Patients taking antidepressants who have not been on a stable dose of their antidepressant for at least 12 weeks prior to Screening; for patients on a stable dose of their antidepressant for at least 12 weeks prior to Screening, must agree to continue their stable dose for the duration of the Double-Blind Treatment Phase of the study. Dose adjustments will be permitted in the OLE Phase. In the Double-Blind Treatment Phase of the study, antidepressants that are strong CYP2D6 inhibitors are exclusionary (Section 5.7.2).
9. Has a history of sleep-disordered breathing or another underlying sleep disorder that in the opinion of the Investigator is a main contributory factor to the patient's EDS.
10. Has a diagnosis of ESRD (eGFR of <15 mL/minute/1.73 m^2) or severe hepatic impairment (Child-Pugh C).
11. Has a diagnosis of moderate or severe renal impairment (eGFR ≥15 to ≤59 mL/minute/1.73 m^2) or moderate hepatic impairment (Child-Pugh B) at Screening or during the Double-Blind Treatment Phase.
12. Has a family history of sudden cardiac death, unexplained death, or death from a primary dysrhythmia potentially associated with QT prolongation in any family member (i.e., first degree relative such as parent, sibling, or offspring).
13. Has a history of unexplained syncope.
14. Has a history of long corrected QT interval (QTc) syndrome or corrected QT interval using Fridericia's formula (QTcF) >450 msec for males or >470 msec for females (QTcF = QT / 3√ RR) sustained atrial fibrillation (AF) or left ventricular ejection fraction <50%.

15. Has a history of documented symptomatic arrhythmias (e.g., ECG, Holter monitor).
16. Electrocardiogram abnormalities during a 10-second, 12-lead ECG at Screening of first degree AVB (PR interval >220 msec), QRS >120 msec, heart rate (HR) <50 beats per minute (bpm), marked T-wave abnormalities, more than single atrial premature complexes (APCs) or premature ventricular contractions (PVCs), left bundle branch block, or Brugada pattern type 1.

    Note: Patients with 1st degree AVB with a PR interval ≥220 msec, who are treated prophylactically with an allowable implanted device are not excluded from the study.

17. Based on Holter monitor, any episode of 3rd degree AVB, any prolonged episode of second degree AVB (>2 episodes during waking hours, >6 episodes during sleep), any prolonged episode of 2nd degree AVB (>10 seconds), any asystole longer than 3.5 seconds, any run of ventricular tachycardia (VT) >6 beats, frequent runs of non-sustained VT (>5/24 hour), >400 PVCs/24 hours, AF or paroxysmal AF, or frequent or complex atrial arrhythmias.
18. Has history of New York Heart Association (NYHA) class III or class IV heart failure.
19. Has an implanted defibrillator or implanted biventricular pacemaker.

    Note: Patients with implanted univentricular pacemakers that are used prophylactically to prevent or treat bradycardia or heart block may be included.

20. Is receiving a medication known to prolong the QT interval.
21. Has a history of clinically significant hypokalemia or hypomagnesemia that cannot be adequately controlled by supplementation.
22. Has serum potassium or magnesium levels that are outside of the normal reference ranges and considered clinically significant at Screening. Patients with mild hyperkalemia that, in the opinion of the Investigator, does not pose an arrhythmia threat may be included.
23. Is receiving a concomitant medication that is known to be a strong CYP2D6 inhibitor, a strong CYP3A4 inducer; or a centrally acting histamine 1 receptor (H_1R) antagonist (sedating antihistamine).

    Note: Patients who undergo a washout of these medications of at least 5 half-lives may be enrolled in the Double-Blind Treatment Phase of the study.
    Note: Use of strong CYP2D6 inhibitors and strong CYP3A4 inducers is allowed during the OLE Phase; however, adjustment of pitolisant dose is required (Section 3.1.2.2). Although not prohibited during the OLE Phase of the study, use of centrally acting or sedating H_1R antagonists should be avoided.

24. Is a known CYP2D6 PM.
25. Regular use (more than twice per week) of any sleep-promoting treatments that could affect EDS and not willing to limit use to no more than twice per week during Screening and for the duration of the Double-Blind Treatment Phase of the study (use of sleep-promoting agents are not allowed within one day prior to study-related assessments).

26. Has abnormal laboratory values at Screening that are clinically significant as determined by the Investigator.
27. Has initiated any new or change in allied health therapies or interventions that can interfere with the study outcomes within 28 days prior to randomization and that are prohibited during the Double-Blind Treatment Phase of the study, based on the Investigator's judgment.
28. Has a current or recent (within 1 year) history of a substance use disorder or dependence disorder, including alcohol and caffeine use disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).
29. Has planned surgery during the Double-Blind Treatment Phase of the study; planned surgery is permitted during the OLE Phase.
30. Has a significant risk of committing suicide or suicidality based on history, routine psychiatric examination, Investigator's judgment, or who has an answer of "yes" on any question other than questions 1 to 3 on the C-SSRS (Appendix C).
31. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to an unstable or uncontrolled medical condition or one that might interfere with the conduct of the study, confound interpretation of study results, pose a health risk to the patient, or compromise the integrity of the study.

4.2. Method of Assigning Patients to Treatment Groups

Patients who meet all eligibility criteria will be randomized to treatment and will be assigned a unique identification (ID) number prior to dosing using interactive response technology (IRT). Randomization will be stratified by concomitant use of wake-promoting agents. Medications that are considered wake-promoting agents are:

- Solriamfetol/Sunosi
- Modafinil/Provigil
- Armodafinil/Nuvigil
- Lisdexamfetamine dimesylate/Vyvanse
- Dexmethylphenidate/Focalin
- Methylphenidate/Adhansia, Aptensio, Concerta, Cotempla, Daytrana, Jornay, Metadate, Methylin, Quillichew, Quillivant, Ritalin
- Amphetamine and amphetamine salts/Adderall, Adzenys, Desoxyn, Dexedrine, Dyanavel, Eveko, Mydayis, Procentra, Zenzedi

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

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

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

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

4.3. Blinding

For the Double-Blind Treatment Phase of the study, patients, Investigators, personnel involved in the conduct and interpretation of the study, site personnel involved in safety and efficacy assessments, and Sponsor staff will be blinded to the treatment assignments.

Blinding is not applicable in the OLE Phase of the study.

4.3.1. Breaking the Blind

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

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

All circumstances leading to the premature unblinding must be clearly documented.

4.4. Patient Withdrawal and Follow-up

4.4.1. Patient Withdrawal

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

Possible reasons for early withdrawal include:

- AE
- Lack of effect (LOE)
- Patient decision
- Lost to follow-up
- No longer meets eligibility criteria
- Non-compliance with study protocol
- Non-compliance with study treatment

- Other, with specific reason (e.g., pregnancy)

Any ECG finding that demonstrates QT prolongation (i.e., QTcF >500 msec or an increase >60 msec regardless of resultant QTc value) should be promptly addressed by the Investigator and will require discontinuation of study drug. Other ECG abnormalities may require discontinuation of study drug based on Investigator discretion, in consultation with the Medical Monitor, as detailed in Section 6.3.4.2.

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

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

The date and the primary reason for early withdrawal will be recorded in the electronic case report form (eCRF). At the time of withdrawal from the study, every attempt should be made to complete the Early Termination (ET) Visit assessments (Section 7.2.5 and Section 7.3.2.5).

4.4.2. Temporary Withdrawal of Study Drug During the Open-Label Extension Phase

As noted in Section 6.3.4.2, in the event of clinically significant ECG findings (other than those that require discontinuation of study drug treatment [Section 4.4.1]), in consultation with the Medical Monitor, the Investigator may decide to temporarily stop (interrupt) pitolisant dosing for 2 to 3 days. A follow-up ECG should be performed within 24 hours and again 7 days later to ensure the abnormality is not worsening. Follow-up 12-lead ECGs may be performed locally, with the results sent to the Investigator. Upon resolution of the ECG abnormality, pitolisant administration may resume at the same dose as before the interruption, or the pitolisant dose may be lowered by 50%. If the condition persists after the interruption in dosing, the Investigator, in consultation with the Medical Monitor, will decide whether treatment should be permanently discontinued.

4.4.3. Procedures for Patient Follow-up

All patients who complete the Double-Blind Treatment Phase of the study are required to undergo the safety assessments outlined in the EOT Visit (Section 7.2.4.4). Patients who prematurely discontinue study drug during the Double-Blind Treatment Phase are required to undergo the safety assessments outlined in the ET Visit, and the reasons for discontinuation must be recorded (Section 7.2.5). Additionally, patients in the Double-Blind Treatment Phase who do not enter the OLE Phase will be contacted by telephone 15 (±3) days and 30 (+3) days after taking the final dose of blinded study drug to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use (Safety Follow-up TCs; Section 7.4).

All patients who complete the optional OLE Phase of the study are required to undergo the safety assessments outlined for the EOT Visit (Section 7.3.2.4). Patients who prematurely discontinue study drug during the OLE Phase are required to undergo the safety assessments outlined in the

ET Visit, and the reasons for discontinuation must be recorded (Section 7.3.2.5). Additionally, patients in the OLE Phase will be contacted by telephone 15 (±3) days and 30 (+3) days after taking the final dose of open-label pitolisant to assess AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use (Safety Follow up TCs; Section 7.4).

Every effort should be made to educate patients on the importance of remaining in the study and attending scheduled study visits, including those required after early discontinuation of study drug.

4.4.4. Withdrawal of Consent for Contact

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

4.4.5. Patients Deemed Lost to Follow-up

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

4.5. Patient Replacement

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

4.6. Study and Patient Completion

4.6.1. Study Completion

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

The OLE Phase of the study will continue until either the last patient completes the EOT Visit (Visit 8) after the final dose of open-label treatment or the Sponsor elects to terminate the study.

4.6.2. Patient Completion

Patients who complete the EOT Visit in the Double-Blind Treatment Phase will be considered to have completed the study. The OLE Phase of the study is optional and patients who complete an EOT Visit (Visit 8, or earlier in the event the Sponsor terminates the study prior to a patient's Visit 8) in the OLE Phase will be considered to have completed the study.

4.7. Screen Failures

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

Patients who do not meet the eligibility criteria at the Screening/Baseline Visit will be screen-failed without receiving study drug but may be rescreened once for study entry.

If a patient is re-screened for enrollment, a new informed consent form (ICF) must be signed, and a new patient number will be assigned by the IRT system. If the patient is out of the initial 45-day screening window, all screening procedures must be repeated except for the genetic test confirming DM1.

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

5. STUDY TREATMENT

Study drug, defined as pitolisant (investigational product) or placebo (comparator), will be provided by the Sponsor. All patients should take their study drug once daily in the morning upon wakening, unless otherwise specified (Section 7.2.4.1 and Section 7.2.4.4).

5.1. Description of Treatments

5.1.1. Pitolisant (Investigational Product)

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

- Pitolisant 4.45 mg tablets: white, round, plain, biconvex film-coated tablet, 3.7 mm diameter. Each tablet contains 5 mg of pitolisant hydrochloride equivalent to 4.45 mg of pitolisant.
- Pitolisant 17.8 mg tablets: white, round, plain, biconvex film-coated tablet, 7.5 mm diameter. Each tablet contains 20 mg of pitolisant hydrochloride equivalent to 17.8 mg of pitolisant.

5.1.2. Placebo (Comparator)

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

5.2. Manufacturing, Packaging, and Labeling

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

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

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

The Double-Blind Treatment kit will consist of three boxes, one box for the Titration Period (titration sub-kit; contains three smaller boxes, one for each week) and two boxes for the Stable Dose Period (stable dosing sub-kits; one box containing supplies for Days 22 to 49 and a second box containing supplies for Days 50 to 77).

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

- Titration sub-kit:
  - Week 1 – Two 10-count bottles, one labeled “A” and one labeled “B” for Week 1 (Days 1 to 7), containing pitolisant 4.45 mg or matching placebo tablets
  - Week 2 – Two 20-count bottles, one labeled “A” and one labeled “B” for Week 2 (Days 8 to 14), containing pitolisant 4.45 mg or matching placebo tablets
  - Week 3 – Two 10-count bottles, one labeled “A” and one labeled “B” for Week 3 (Days 15 to 21), containing pitolisant 17.8 mg or matching placebo tablets

- Stable dosing sub-kits:
  - Weeks 4 through 7 – Two 30-count bottles, one labeled "A" and one labeled "B" for Weeks 4 to 7 (Days 22 to 49), containing pitolisant 17.8 mg or matching placebo tablets
  - Weeks 8 through 11 – Two 30-count bottles, one labeled "A" and one labeled "B" for Weeks 8 to 11 (Days 50 to 77), containing pitolisant 17.8 mg or matching placebo tablets

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

Study drug dosing in the OLE Phase will be as described in Table 7. Study drug for the OLE Phase will be provided to patients as individual bottles for both the OLE Titration Period and the OLE Long-Term Dosing Period.

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

5.3. Storage

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

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

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

5.4. Study Drug Administration

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

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

During the Double-Blind Treatment Phase, patients will take study drug (pitolisant or placebo) once daily in the morning upon wakening in accordance with their randomized dose, as detailed in Table 6. Patients will be instructed to record in the study drug dosing section of the study diary the number of tablets taken from each bottle daily; the time of study drug dosing will be recorded in the diary on the day prior to Visits 3 and 5.

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

During the OLE Phase, patients will take open-label pitolisant once daily in the morning upon wakening as detailed in Table 7.

5.5. Study Drug Compliance

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

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

Study drug compliance during the OLE Phase will be monitored during on-site visits by conducting tablet counts based on the returned study drug. During the OLE TCs, compliance will be monitored by confirming the current dose of study drug being taken by the patient as well as shipment/receipt of study drug in a quantity sufficient for 3 months (i.e., 90 days) of once daily administration.

5.6. Study Drug Accountability

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

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

5.7. Prior and Concomitant Therapy

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

All medications taken by patients between signing of informed consent and the second Safety Follow-Up TC (30 +3 days after final dose of study drug, Section 7.4) will be recorded, including dose, regimen, reason for administration, and start date. Changes in concomitant medication will be recorded in the eCRF. Nonpharmacologic therapies/procedures and changes in therapies/procedures will also be recorded in the eCRF. Any prior or concomitant medication used to treat seizure disorders should be recorded on the eCRF.

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

5.7.1. Permitted Concomitant Medications

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

Except for the prohibited medications specified in Section 5.7.2, patients will be allowed to continue medications for the treatment of DM or other comorbidities as currently prescribed by their physicians. Wake-promoting agents including mixed amphetamine salts such as Vyvanse (lisdexamfetamine dimesylate), Adderall (amphetamine and dextroamphetamine) and similar agents that are prescribed to treat EDS are permitted. The use of hypnotics is allowed up to 2 nights per week, but they are not allowed the night prior to any efficacy assessment.

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

5.7.2. Prohibited Medications

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

The use of strong CYP2D6 inhibitors or strong CYP3A4 inducers is not permitted during the Double-Blind Treatment Phase of the study, and if being used, should be discontinued at Screening; washout of 5 half-lives of these medications is required prior to enrollment and initiating study drug. These medications are allowed during the OLE Phase of the study, but adjustment of the dose of pitolisant is required (Section 5.7.3).

Pitolisant increases the levels of histamine in the brain; therefore, centrally acting H_1R antagonists (sedating antihistamines) that cross the blood-brain barrier may reduce the effectiveness of pitolisant. Concomitant use of centrally acting or sedating H_1R antagonists is not permitted during the Double-Blind Treatment Phase of the study (requires a washout of 5 half-lives prior to randomization). Although not prohibited during the OLE Phase of the study, use of these medications should be avoided and, if needed, will require consultation with the Medical Monitor.

Examples of centrally acting or sedating H_1R antagonists, strong CYP2D6 inhibitors, strong CYP3A4 inducers, and medications that may prolong the QT interval are provided in Appendix E.

5.7.3. Medications Requiring Adjustment to the Dose of Pitolisant

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

- Strong CYP2D6 inhibitors: Systemic exposure of pitolisant is increased 2.2-fold in the presence of strong CYP2D6 inhibitors. If initiating treatment with a strong CYP2D6 inhibitor during the OLE Phase, pitolisant dose should be reduced by half.
- Strong CYP3A4 inducers: Systemic exposure of pitolisant is reduced by 50% in the presence of strong CYP3A4 inducers. If initiating treatment with a strong CYP3A4 inducer during the OLE Phase, clinical response should be monitored, and pitolisant

dose may need to be increased. Pitolisant dose may only be increased up to the maximum permitted dose of 35.6 mg daily.

Procedures for pitolisant dose adjustments in the OLE Phase are provided in Section 3.1.2.2.

6. STUDY PROCEDURES AND ASSESSMENTS

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

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history (including any history of seizure disorder and hospitalizations) will be obtained at Screening to ensure patients qualify for the study and will be updated at the Baseline Visit if needed and as necessary thereafter. Confirmation of a patient's diagnosis of DM1 will be obtained via review of the patient's medical records; genetic testing will be performed during Screening to confirm CTG repeat of ≥100.

6.1.2. Demographics

Demographic information collected will include date of birth, sex, race, and ethnicity. In addition, a patient's current employment status will be recorded in the eCRF.

6.2. Efficacy Assessments

Patients will be assessed for efficacy using validated scales, assessments, and questionnaires. Various symptoms of DM1 will be evaluated, including those related to EDS, fatigue, and cognitive functioning. The order of administering efficacy assessments is: DSS, FSS, Cogstate Detection Test, Cogstate Identification Test, Cogstate One-back Test, MDHI, ESS, PGI-S, and SART. The CGI-S will be assessed by the Investigator. The optional MWT will occur based on scheduling with the study site's sleep lab.

6.2.1. Daytime Sleepiness Scale

The DSS is a questionnaire in which patients are asked to assess five items with scores of never (0), seldom (1), often (2), and always (3), one of which is scored in the reverse order. The DSS score can vary from 0 to 15 and the higher the score, the higher the degree of sleepiness. It was developed and validated in patients with DM1 in three sub-groups: early adult-onset (onset of symptoms from 11-20 years old), adult (onset of symptoms from 21-40 years old) and mild (onset of symptoms at >40 years old). The instrument has demonstrated construct (factorial) validity (Laberge et al 2004), convergent and discriminant validity (Laberge et al 2009; Laberge and Dauvilliers 2010) and responsiveness (Laberge et al 2022). The DSS is provided in Appendix F.

6.2.2. Fatigue Severity Scale

The FSS is a 9 item Patient Reported Outcome assessment that covers physical, social, and cognitive effects of fatigue such as function, work, and motivation (Krupp et al 1989). The 9 items are summed and then averaged to produce a global score. Each item has seven choices from strongly disagree to strongly agree (1-7), and the recall period is the past week. The FSS takes approximately 2-3 minutes to complete. It has demonstrated content, construct, and

criterion validity and has demonstrated the ability to detect change (Hewlett et al 2011). The FSS has been used to evaluate fatigue in patients with DM (Hermans et al 2013; Laberge et al 2009). The FSS is provided in Appendix G.

6.2.3. Cogstate Computerized Cognitive Battery Tests

Cognition will be assessed using the Cogstate Computerized Cognitive Battery Tests, a standardized, fully automated, modular battery of tests designed specifically for repeated assessment with minimal practice effects (Collie et al 2003; Falleti et al 2006). The test battery has a short administration time, contains multiple alternate forms, and yields data appropriate for detecting cognitive change. In this study, the cognitive domains of psychomotor function, attention, and working memory will be assessed using the Detection, Identification, and One Back tests, respectively. Patients will undergo two short training sessions to become familiar with the test.

6.2.3.1. Cogstate Detection Test (Psychomotor Function)

The Cogstate Detection Test is a computerized measure of psychomotor function and uses a validated simple reaction time (RT) paradigm with playing card-like stimuli displayed on a computer screen. In this test, the playing cards all depict the same image. The patient is asked to press the "yes" key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response. The main outcome measure for the test is speed of performance (mean of the log10-transformed reaction times for correct responses). Decreasing scores represent improved test performance.

6.2.3.2. Cogstate Identification Test (Attention)

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

6.2.3.3. Cogstate One Back Test (Working Memory)

The Cogstate One Back Test is a computerized measure of working memory and uses a validated n-back paradigm with playing card stimuli displayed on a screen. The patient is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The patient responds by pressing the "yes" or "no" key. The software measures the speed and accuracy of each response.

6.2.4. Myotonic Dystrophy Health Index

The MDHI is a disease-specific, patient-reported outcome measure for DM1. This instrument has been validated in a manner consistent with the FDA guidance on patient reported outcomes and is designed to accurately reflect the overall burden of disease from the patient's perspective. It

focuses on the major symptoms experienced by patients with DM1 and prioritizes them by their relative importance to patients. It is scored on a scale of 0-100, with a higher score representing a higher burden of disease; subscales within the instrument are weighted so that certain themes, including sleep, fatigue, and cognitive impairment, have greater impact on the overall score. (Heatwole et al 2014 and Heatwole et al 2016). Overall, the MDHI is optimally suited to detect small but clinically relevant changes in several key areas of DM health over the course of a treatment trial and has been recognized by the DM working group of National Institute of Neurological Disorders and Stroke (NINDS) as one of the key assessments that should be used in clinical trials of patients with DM1 (NINDS 2014). The MDHI addresses several areas of health relevant to the condition. The tool consists of multiple symptom-related questions grouped into several themes including fatigue, sleep, and cognitive impairment. Subscales of the MDHI measure patients' perception of their health as it relates to mobility, upper extremity function, ability to do activities, fatigue, pain, gastrointestinal issues, vision, communication, sleep, emotional issues, cognitive impairment, social satisfaction, social performance, myotonia, breathing, swallowing, and hearing. The MDHI is provided in Appendix H.

6.2.5. Epworth Sleepiness Scale

The ESS is a questionnaire with eight questions in which respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing or falling asleep while engaged in eight different activities. The questionnaire is a validated measure with high specificity and sensitivity for assessing subjective sleepiness in narcolepsy (Johns 1991). It has been deemed appropriate for the assessment of EDS in patients with DM1 by the NINDS and is recommended for use in this population (NINDS 2014). The total ESS score (sum of 8 item scores) can range from 0 to 24; the total score gives an estimate of the person's 'average sleep propensity' (ASP), across a wide range of activities in their daily lives. The higher the ESS score, the higher that person's ASP in daily life or their 'daytime sleepiness'. The ESS is provided in Appendix I.

6.2.6. Clinical Global Impression of Severity of Excessive Daytime Sleepiness

The CGI-S is a one-item, 4-point Likert-type rating scale and is a widely used assessment in clinical psychopharmacology trials to assess severity of illness. At Baseline, Week 11/EOT in the Double-Blind Treatment Phase, and at each on-site study visit in the OLE Phase, the Investigator will rate his/her impression of the severity of the patient's current overall clinical status related to EDS relative to the Investigator's experience with this patient population, based on observed and reported symptoms and function. The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, please rate the patient's overall severity of EDS at this time". The responses for this investigator-completed scale range from "none" to "severe". The CGI-S is provided in Appendix J.

6.2.7. Patient Global Impression of Severity of Excessive Daytime Sleepiness

The PGI-S is a one-item, 4-point Likert rating scale completed by the patient to rate their overall impression of their EDS. At Baseline, Week 11/EOT in the Double-Blind Treatment Phase, and at each on-site study visit during the OLE Phase, patients will be asked to rate their impression of the overall severity of their symptoms of EDS over the past week, based on the impact EDS has on the patient's ability to function during the day. The PGI-S of EDS asks the patient to rate their likelihood of falling asleep during daytime activities over the past week. The responses for the

patient-completed scale range from “none” to “high” The PGI-S for EDS is provided in Appendix K.

6.2.8. Sustained Attention to Response Task

The SART is a measure of sustained attention, which is the ability to focus on an activity or stimulus over a long period of time, or to direct focus and cognitive ability on specific stimuli. It is a computer-based go/no-go task that requires participants to withhold behavioral response to a single, infrequent target presented amongst a background of frequent non-targets. Both accuracy and response speed, quantified as RT, are important. The SART was developed to investigate lapses of sustained attention in individuals with neurological impairment. It also proved to be a useful tool to investigate sustained attention in a number of other clinical conditions including sleep disorders (van Schie et al 2012). Validation of the SART was done in patients with narcolepsy and is based on a comparison between patients with narcolepsy and healthy controls (Fronczek et al 2006). The SART is also considered a useful tool to measure treatment efficacy in narcolepsy (van der Heide et al 2015).

6.2.9. Maintenance of Wakefulness Test

The MWT, a daytime polysomnographic procedure for the evaluation of daytime somnolence/wakefulness, is used to assess an individual’s ability to stay awake while resisting the pressure to fall asleep. It is used clinically in disorders with excessive somnolence such as narcolepsy and sleep apnea syndrome (Browman et al 1983; Browman et al 1986; Poceta et al 1992; Sangal et al 1992a). The MWT evaluates the magnitude of sleepiness in relationship to the underlying wakefulness system’s functioning. It has also been utilized to examine treatment efficacy (Sangal et al 1992b). When conducting the MWT, patients are administered four 40-minute sessions at 2-hour intervals according to the validated standard (Doghramji et al 1997), with the initial session beginning two hours after wakening.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs, regardless of causality or seriousness, will be collected from the time the patient provides written informed consent through 30 days after the final dose of study drug (Safety Follow-up TC, Section 7.4). Adverse event recording at the Safety Follow-up TCs will include inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]). Additional safety information, including the definition of an AE/SAE and reporting requirements is provided in Section 8.

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

6.3.2. Physical Examinations

Full or abbreviated physical examinations will be performed at study visits as detailed in Section 7. Full physical examinations will include an evaluation of the head and neck as well as

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

Height and weight will be measured using standardized methods. Height will be recorded at Screening. Body weight will be recorded at Screening (Visit 1), Baseline (Visit 2), EOT (Visit 5), and all on-site study visits during the OLE Phase, as detailed in Section 7.

6.3.3. Vital Signs

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

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

6.3.4. Holter Monitoring and 12-Lead Electrocardiograms

Holter monitoring and triplicate 12-lead ECGs will be performed at Screening and during the Double-Blind Treatment Phase and OLE Phase of the study as detailed in Section 7. The Holter monitoring performed at Screening and the ECGs performed at Screening and Baseline will determine whether an exclusionary CV issue is present, and assessment at later time points during the study is designed to detect any changes in CV parameters and to detect the development of arrhythmias.

A core ECG laboratory will manage all ECG and Holter monitoring activities, including standardization and training of the technical staff at all study sites in proper electrode placement, operation of the hardware, and management of patients during testing. Electrocardiogram and Holter monitoring data will be transmitted electronically to the core laboratory and will be promptly interpreted by trained cardiologists. Pre-specified criteria for QT, QRS duration, AVB, and arrhythmias will trigger immediate notifications.

6.3.4.1. Holter Monitoring

Holter monitoring will be performed during Screening (Visit 1) and Visit 3 (Day 22) during the Double-Blind Treatment Phase. Patients will be fitted with a Holter monitor, which they will wear for 24 hours before returning the device to the study site via courier or directly to the site if able, as detailed in a separate instructional document.

In the OLE Phase, to monitor for arrhythmias at the time patients have reached their 35.6 mg dose of pitolisant, Holter monitoring (24-hour) will be initiated at the end of the OLE Titration Period at Visit 6 (Day 99).

For all abnormal Holter monitor findings considered clinically significant by the Investigator, additional evaluation, including an unscheduled ECG, is required (the ECG can be performed locally); abnormal findings on follow-up ECGs should be addressed as detailed in Section 6.3.4.2.

The Holter monitor must be placed on the patient and continuous recording started as the ECG data will be taken from the Holter monitor recording.

6.3.4.2. 12-Lead Electrocardiograms

Triplicate 12-lead ECGs will be obtained for all patients at every on-site study visit as detailed in Section 7. Patients should be resting for at least 5 minutes before each 12-lead ECG is performed. At Visit 3 and Visit 5, triplicate 12-lead ECGs will be performed with every blood sample collected for PK analyses, as detailed in Section 7.2.4.1 and Section 7.2.4.4, respectively. The ECGs should be done prior to and within 15 minutes of the blood draw for PK analyses.

For clinically significant ECG findings, a follow-up ECG should be performed within 24 hours and again 7 days later to ensure the abnormality is not worsening. Follow-up 12-lead ECGs may be performed locally and sent to the Investigator for assessment; the Investigator will submit all ECGs done locally to the central ECG vendor.

The following ECG abnormalities should be promptly addressed by the Investigator and will require discontinuation of study drug (Section 4.4.1):

- Any ECG finding that demonstrates QT prolongation (i.e., QTcF >500 msec or an increase >60 msec) regardless of resultant QTc value

In addition to a potential QT prolongation, the Medical Monitor should be consulted for:

- PR interval >300 msec, QRS duration >140 msec, or any increase from baseline in PR or QRS greater than 50% or 40%, respectively
- HR increase >65% over baseline or decrease >40% compared with baseline

In the event of these clinically significant abnormal PR interval, QRS duration, or HR ECG results, the ECG should be repeated as soon as possible and if done the next day, attempts should be made to perform the repeat ECG at the same time of day that the abnormal ECG was obtained. If the event persists or worsens, study drug may be interrupted for 2 to 3 days and the ECG will be repeated on the third day. If the abnormality has improved, study drug dosing may resume. If the condition persists or worsens after the study drug interruption, the Investigator, in consultation with the Medical Monitor, will decide whether treatment should be permanently discontinued.

6.3.5. Clinical Laboratory Tests

Clinical laboratory tests will include serum chemistry, hematology, urinalysis, pregnancy tests (serum and/or urine), and urine drug screens as detailed in Table 8. Samples for clinical laboratory tests (serum chemistry and hematology) will be collected as outlined in Section 7.

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

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

Patients will be administered supplements if their serum magnesium and/or potassium values decrease by 20% compared with Baseline or if the levels are in the low normal or below normal range.

The total volume of blood collected is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period (NIH 2009).

Table 8: Clinical Laboratory Tests

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

FCBP = female of child-bearing potential; HbA1C = hemoglobin A1C; WBC = white blood cell.

[a] Patients will be administered supplements if serum magnesium and/or potassium levels decrease by 20% compared with Baseline, or if the levels are in the low normal or below normal range.

NOTE: Parameters will be assessed at study visits as detailed in the Schedule of Assessments for the Double-Blind Treatment Phase and the Schedule of Assessments for the Open-Label Extension Phase.
NOTE: Wake-promoting agents including mixed amphetamine salts such as Vyvanse (lisdexamfetamine dimesylate), Adderall (amphetamine and dextroamphetamine) and similar agents that are prescribed to treat EDS are permitted. Mexilitene may cause a positive urine drug screen for amphetamine. In the event a urine drug screen is positive for amphetamines, consult with the Medical Monitor before screen failing the patient. Hypnotics are permitted during the study (Section 5.7.1).

6.3.6. Additional Safety Assessments

Suicide Risk/Suicidality

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

Seizure Disorder

In patients with a history of seizure disorders, the worsening of seizures or new onset seizures will be reported as AEs and the type, duration, and frequency of occurrence will be recorded in the eCRF.

6.4. Pharmacokinetic Assessments

Blood samples for determination of pitolisant and its major metabolite concentrations (trough and at the time of maximum concentration [t_{max} (3 hours ±30 minutes post dose)]) will be collected during the Stable Dose Period of the Double-Blind Treatment Phase (Visits 3 and 5), as detailed in Section 7.2.4.1 and Section 7.2.4.4, respectively. Triplicate 12-lead ECGs will be performed before each PK sample collection. At Visit 3, the Holter monitor should be placed on the patient and continuous recording started as the 12-lead ECG (in triplicate) data are taken from the Holter monitor recording. The estimated total volume of blood to be drawn on PK sampling days, including samples for PK analyses (4.0 mL per sample), serum chemistry tests (5.0 mL per sample), and hematology tests (4.0 mL per sample) is presented in Table 9. The total volume of blood collected is not to exceed the maximal allowable for adults of 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period (NIH 2009).

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

Table 9: Estimated Total Blood Draw Volumes on Pharmacokinetic Sampling Days

Visit	Blood Sample Volume (mL)			
	PK	Serum Chemistry	Hematology	Total
Visit 3 (Day 22 ±3 days)	4	5	4	13
Visit 5 (Day 77 ±3 days)	4	5	4	13

PK = pharmacokinetics
Note: Serum chemistry and hematology parameters are listed in Table 8.

6.5. Potential Use of Alternative Methods for Completing Study Assessments

To allow for greater flexibility and potentially decrease patient burden related to travel to the study site, specific study assessments may be completed by alternative methods (Table 10).

6.5.1. Assessments that may be Completed Remotely

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

Specific efficacy assessments including administration of the DSS, FSS, MDHI, ESS, CGI-S, and PGI-S may be completed by the Investigator and/or site staff remotely using telemedicine technology.

Other procedures including completing the informed consent process and study drug compliance/accountability review may be completed by the Investigator and/or site staff remotely using telemedicine technology.

6.5.2. Assessments that may be Completed at the Patient's Home

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

- Vital signs
- Abbreviated physical examination
- 12-lead ECG (in triplicate)
- Laboratory assessments
- Other assessments including Holter monitoring and study drug accountability (Table 10)

Visit 3 PK samples may be collected at the next on-site study visit or at an unscheduled visit if not able to be collected earlier.

6.5.3. Other Considerations

The Cogstate Computerized Cognitive Battery Tests, SART, and optional MWT, which are to be completed at the Baseline Visit (Visit 2) and EOT Visit (Visit 5) cannot be completed remotely; therefore, these assessments are required to be completed at the site. Every effort should be made for the Visit 2/Baseline and Visit 5/EOT to be completed at the study site according to the study schedule.

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

Table 10: Alternative Methods for Completing Study Assessments

Assessment Scheduled to be Performed at an On-Site Study Visit	Telemedicine	Performed by a Home Healthcare Professional	Potential to be Conducted at the Next On-Site Study Visit or at an Unscheduled Visit
Informed Consent	X		
Pregnancy Test (FCBP)		X	
Urine Drug Screen		X	

Assessment Scheduled to be Performed at an On-Site Study Visit	Telemedicine	Performed by a Home Healthcare Professional	Potential to be Conducted at the Next On-Site Study Visit or at an Unscheduled Visit
Abbreviated Physical Examination		X	
Vital Signs		X	
12-Lead ECG (in triplicate)		X	
Holter Monitoring[a]		X	
DSS, FSS, MDHI, ESS, CGI-S, PGI-S	X		
Cogstate Detection, Identification, One Back			X
SART			X
Clinical Laboratory Tests		X	
Blood Sample for PK			X
Adverse Events	X	X	
Concomitant Medications	X	X	
C-SSRS	X		
Dispense Study Drug	X		
Study Drug Compliance	X		
Study Drug Accountability	X	X	

[a] When an ECG is also required, Holter monitor should be placed on the patient and continuous recording started as the ECG data are taken from the Holter monitor recording.

CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DSS = Daytime Sleepiness Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; FCBP = female of child-bearing potential; FSS = Fatigue Severity Scale; MDHI = Myotonic Dystrophy Health Index; MWT = Maintenance of Wakefulness Test; PGI-S = Patient Global Impression of Severity PK = pharmacokinetic(s); SART = Sustained Attention to Response Task

7. TIMING OF PROCEDURES AND ASSESSMENTS

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

7.1. Screening (Visit 1)

After providing written informed consent, patients will undergo screening assessments to assess eligibility to participate in the study. Only patients who meet all eligibility criteria will be enrolled. The Screening Period will be for a maximum of 45 days.

Patients will be provided with a sleep diary (Appendix A) and the following evaluations will be performed during the Screening Visit (Visit 1), within 45 days prior to randomization and the first dose of study drug:

- Inclusion/exclusion criteria (Section 4.1)
- Demographics
- Medical history (Section 6.1.1)
- Serum pregnancy test (FCBP only)
- Urine drug screen (Table 8)
- Full physical examination (Section 6.3.2)
- Body weight and height (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 8)
- Genetic testing
- 24-hour Holter monitoring (Section 6.3.4.1)
- 12-lead ECG (in triplicate) (Section 6.3.4.2)
- AEs (since providing written informed consent)
- Concomitant medications (since providing written informed consent)
- Risk of suicide/suicidality (C-SSRS Lifetime Recent; Appendix C)
- Cogstate Detection Test training (Section 6.2.3.1)
- Cogstate Identification Test training (Section 6.2.3.2)
- Cogstate One Back Test training (Section 6.2.3.3)
- MDHI (Section 6.2.4)
- CGI-S for EDS (Section 6.2.6)
- SART training (Section 6.2.8)

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

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

Section 3.1.1.2 provides details on study drug dosing during the 11-week Double-Blind Treatment Phase of the study.

7.2.1. Baseline Visit (Visit 2; Day -3 to Day -1)

The following assessments will be performed on Day -1:

- Review of inclusion/exclusion criteria (patients must meet all eligibility criteria) (Section 4.1)
- Medical history update (Section 6.1.1)
- Urine pregnancy test (FCBP only)
- Urine drug screen (Table 8)
- Abbreviated physical examination (Section 6.3.2)
- Body weight (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis; Table 8)
- 12-Lead ECG (in triplicate) (Section 6.3.4.2)
- Review of AEs (since providing written informed consent)
- Review of concomitant medications (since providing written informed consent)
- C-SSRS (Since Last Update; Appendix D)
- Optional MWT (Section 6.2.9) (to be performed only for those patients who provide written informed consent and are successfully scheduled for this assessment; these patients must return to the study site before the scheduled MWT); the MWT Baseline assessment may be performed up to 3 days in advance of Day 1
- DSS (Section 6.2.1)
- FSS (Section 6.2.2)
- Cogstate Detection Test (Section 6.2.3.1)
- Cogstate Identification Test (Section 6.2.3.2)
- Cogstate One Back Test (Section 6.2.3.3)
- MDHI (Section 6.2.4)
- ESS (Section 6.2.5)
- CGI-S of EDS (Section 6.2.6)
- PGI-S of EDS (Section 6.2.7)

- SART (Section 6.2.8)

Patients who meet all eligibility criteria at the Baseline Visit will be randomized at a 1:1:1 ratio to receive treatment with lower dose pitolisant, higher dose pitolisant, or matching placebo as detailed in Section 3.1.1.2.

Eligible patients will be dispensed a study drug dosing diary and study drug sub-kit for titration for Week 1 through Week 3; patients will be instructed to take study drug once daily in the morning upon wakening and to record daily the date and number of tablets of study drug taken (Section 5.4.1 and Appendix B).

Patients will receive study drug after completion of Day -1 assessments and will be instructed to take their first dose of study drug on the morning after they receive their study drug from the site (i.e., the first day of study drug dosing is Day 1).

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

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

Eligible patients will be titrated to their randomized dose during a 3-week Titration Period. First day of blinded treatment will be on the day following the Baseline Visit (Day 1) and study drug dose will be titrated on Day 8 and again on Day 15; all patients will be at their randomized dose of study drug by Day 15 (Table 6).

7.2.3. Telephone Contacts (TC 1 and TC 2) (Days 8 and 15 ±3 Days)

After completion of the Baseline Visit (Day -1), no additional on-site study visits are scheduled during the Titration Period in the Double-Blind Treatment Phase. Patients will be contacted by the study site by telephone on Days 8 and 15 (±3 days; TCs 1 and 2, respectively) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug dose.

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

Patients will continue to take study drug at their randomized dose during the Stable Dose Period in the Double-Blind Treatment Phase and will return to the study site on Days 22, 49, and 77 (±3 days; Visits 3, 4, and 5, respectively) for safety and efficacy assessments. Pharmacokinetic assessments will be performed on Visits 3 and 5. Patients will be contacted by the study site by telephone on Day 28 (±3 days; TC 3). The last dose of blinded treatment is on Day 77 ±3 days (Visit 5; EOT Visit in the Double-Blind Treatment Phase).

7.2.4.1. Visit 3 (Day 22 ±3 Days)

To accommodate PK sample collection at Visit 3, patients will be instructed to not take their daily dose of study drug before arriving at the study site; patients will bring their study drug and study diary with them to the study visit (time of study drug administration on the day before Visit 3 should be recorded in the study diary).

Study drug administration will be at the study site and timing will be based on timing of the PK sampling and 12-lead ECGs.

12-lead ECGs and blood sample collection for PK analyses:

- Holter monitor should be placed on the patient and continuous recording started as ECG data are taken from the Holter recording.
- 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses will be performed before study drug is administered (the time of the ECG and blood sample collection for PK must be recorded). The ECGs should be done prior to and within 15 minutes of the pre-dose blood sample collection for PK analyses.
- After the 12-lead ECGs and PK sample collection are completed, patients will be administered study drug (the time of study drug administration must be recorded).
- Additional 12-lead ECGs and blood sample collection for PK analyses will be performed at 3 hours (±30 minutes) after dosing (the time of each ECG and blood sample collection for PK must be recorded). The ECGs should be done prior to and within 15 minutes of the post-dose blood sample collection for PK analyses.

The following assessments will also be performed at Visit 3:

- Urine pregnancy test (FCBP only)
- Abbreviated physical examination (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Table 8)
- Review of AEs
- Review of concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)
- 24-hour Holter monitoring

Patients will be dispensed study drug in a sub-kit for Week 4 through Week 7.

7.2.4.2. Telephone Contact (TC 3) (Day 28 ±3 Days)

Patients will be contacted by the study site by telephone on Day 28 (±3 days; TC 3) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and confirm compliance with administration of study drug.

7.2.4.3. Visit 4 (Day 49 ±3 Days)

The following assessments will be performed at Visit 4:

- Urine pregnancy test (FCBP only)

- Abbreviated physical examination (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Table 8)
- 12-Lead ECG (in triplicate) (Section 6.3.4.2)
- Review AEs
- Review concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- DSS (Section 6.2.1)
- FSS (Section 6.2.2)
- MDHI (Section 6.2.4)
- ESS (Section 6.2.5)
- CGI-S of EDS (Section 6.2.6)
- PGI-S of EDS (Section 6.2.7)

Patients will be dispensed study drug in a sub-kit for Week 8 through Week 11.

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

Visit 5 (Day 77 ±3 days) is the EOT Visit in the Double-Blind Treatment Phase of the study.

To accommodate PK sample collection at Visit 5, patients will be instructed to not take their daily dose of study drug before arriving at the study site; patients will bring their study drug and study diary with them to the study visit (time of study drug administration on the day before Visit 5 should be recorded in the study diary).

Study drug administration will be at the study site and timing will be based on timing of the PK sampling and 12-lead ECGs.

12-lead ECGs and blood sample collection for PK analyses:

- 12-lead ECGs (in triplicate) and a blood sample collection for PK analyses will be performed before study drug is administered (the time of the ECG and blood sample collection for PK must be recorded).
- After the 12-lead ECGs and PK sample collection are completed, patients will be administered study drug (the time of study drug administration must be recorded).
- Additional 12-lead ECGs and blood sample collection for PK analyses will be performed at 3 hours (±30 minutes) after dosing (the time of each ECG and blood sample collection for PK must be recorded). The 12-lead ECGs should be conducted prior to and within 15 minutes of blood sample collection for PK analyses.

The following assessments will also be performed at Visit 5:

- Urine pregnancy test (FCBP only)

- Urine drug screen (Table 8)
- Full physical examination (Section 6.3.2)
- Body weight (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Table 8)
- Review of AEs
- Review of concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- Optional MWT (Section 6.2.9)
  - If a patient enrolled prior to protocol Amendment 4 (i.e., had MWT Baseline assessment) the MWT at Week 11 must be performed.
  - If a patient enrolled after protocol Amendment 4 was implemented, this is an optional assessment, to be conducted only for those patients who provide written informed consent.
  - The EOT (Week 11) MWT assessment should not be performed on the same day as the Visit 5 PK as patients will take their dose of study drug at the site after ECGs and the pre-dose PK blood draw are done. The EOT (Week 11) MWT may be conducted up to 3 days in advance of Day 77; patients should take their dose of study drug on the morning of the scheduled Week 11 MWT assessment.
- DSS (Section 6.2.1)
- FSS (Section 6.2.2)
- Cogstate Detection Test (Section 6.2.3.1)
- Cogstate Identification Test (Section 6.2.3.2)
- Cogstate One Back Test (Section 6.2.3.3)
- MDHI (Section 6.2.4)
- ESS (Section 6.2.5)
- CGI-S of EDS (Section 6.2.6)
- PGI-S of EDS (Section 6.2.7)
- SART (Section 6.2.8)

Patients will be given the opportunity to participate in the OLE Phase at this visit. Eligible patients who enter the optional OLE Phase will be dispensed OLE pitolisant for titration (Section 5.4.2); eligibility criteria must be confirmed before patients receive open-label pitolisant. Patients will be instructed to begin taking open-label pitolisant on the following day in the morning upon wakening (Day 78 ±3 days).

Patients who do not enter the OLE Phase will receive Safety Follow-up TCs from the study site 15 (± 3) days and 30 (+3) days after last dose of blinded treatment, as outlined in Section 7.4.

7.2.5. Early Termination Visit for Double-Blind Treatment Phase

Every effort should be made to perform the ET evaluations for patients who terminate early from the Double-Blind Treatment Phase of the study. At the ET Visit, the reason for early termination must be recorded. The safety and efficacy evaluations to be performed at the ET Visit are the same as those listed for Visit 5 (Section 7.2.4.4).

Patients who discontinue from the Double-Blind Treatment Phase prior to Day 77 may not enroll in the OLE Phase of the study.

7.3. Open-Label Extension Phase (Day 78 to End-of-Treatment)

Eligible patients who enter the OLE Phase of the study will begin a 3-week titration period after completion of the Double-Blind Treatment Phase. The Titration Period for the OLE will start on Day 78 (±3 days) and will end on Day 98 (±3 days); the Long-Term Dosing Period will start on Day 99 (±3 days) and will end at Day 459/Month 15 (EOT; Visit 8) for each patient unless the patient withdraws from the study early or the Sponsor elects to terminate the study.

Section 3.1.1.3 provides details on study drug dosing for the OLE Phase of the study. Dose adjustments are permitted in the OLE Phase; pitolisant dose can be adjusted (higher or lower) based on Investigator assessment of tolerability as outlined in Section 3.1.2.2.

7.3.1. Titration Period; Open-Label Extension Phase (Days 78 to Day 98)

Patients will be titrated to a 35.6 mg dose of open-label pitolisant during the 3-week Titration Period as detailed in Table 7. Patients will receive their first dose on Day 78 (±3 days); pitolisant dose will be titrated on Day 85 (±3 days) and again on Day 92 (±3 days), with patients reaching a dose of 35.6 mg (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability) by Day 92; dose adjustments are permitted (Section 3.1.2.2).

No study visits are scheduled during the OLE Titration Period. Patients will be contacted by the study site by telephone on Days 85 and 92 (±3 days; TCs 4 and 5, respectively) to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use, complete the C-SSRS, and review/confirm titration of study drug.

7.3.2. Long-Term Dosing Period, Open-Label Extension Phase (Day 99 to End of Treatment)

Patients will continue to take open-label pitolisant (35.6 mg or their maximum dose up to 35.6 mg based on Investigator assessment of tolerability) during the OLE Long-Term Dosing Period as detailed in Table 7, with dosing adjustments permitted as described in Section 3.1.2.2.

The Long-Term Dosing Period will begin on Day 99 (±3 days); patients will have an on-site study visit on that day (Visit 6; Section 7.3.2.1) followed by alternating follow-up TCs to assess safety (Section 7.3.2.2) and on-site study visits approximately every 3 months (90 days ±7 days) to assess safety and effectiveness (Section 7.3.2.3). This pattern of alternating TCs and on-site

study visits will be repeated until Day 459/Month 15 (Visit 8) unless the patient withdraws from the study early or the Sponsor elects to terminate the study.

7.3.2.1. Visit 6 (Day 99 ±3 Days)

Patients will return to the study site on Day 99 (±3 days); the following assessments will be performed:

- Urine pregnancy test (FCBP only)
- Urine drug screen (Table 8)
- Full physical examination (Section 6.3.2)
- Body weight (Section 6.3.2)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Table 8)
- Vital signs (Section 6.3.3)
- 12-lead ECG (in triplicate) (Section 6.3.4.2)
- 24-hour Holter monitoring (Section 6.3.4.1)
- Review of AEs
- Review of concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- DSS (Section 6.2.1)
- FSS (Section 6.2.2)
- Cogstate Detection Test (Section 6.2.3.1)
- Cogstate Identification Test (Section 6.2.3.2)
- Cogstate One Back Test (Section 6.2.3.3)
- MDHI (Section 6.2.4)
- ESS (Section 6.2.5)
- CGI-S of EDS (Section 6.2.6)
- PGI-S of EDS (Section 6.2.7)
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

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

7.3.2.2. Telephone Contacts; Day 189 (±7 Days; TC 6) and Day 369 (±7 days; TC 7)

Patients will receive a TC from the study site on Day 189 (±7 days) and approximately 6 months later (Day 369 ±7 days) unless the patient withdraws from the study early or the Sponsor elects to terminate the study.

The following will be recorded at each TC:

- Review AEs
- Review concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- Confirm shipment/receipt of the next 3-month (90-day) supply of study drug
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

Additional unscheduled TCs may be conducted as needed to discuss potential dose changes, arrange for shipment of additional study drug, if necessary, report AEs, or to complete other assessments if clinically indicated in the opinion of the Investigator.

7.3.2.3. Visit 7 (Day 279 [±7 Days])

Patients will undergo the following assessments at on-site study visits:

- Urine pregnancy test (FCBP only)
- Urine drug screen (Table 8)
- Full physical examination (Section 6.3.2)
- Body weight (Section 6.3.2)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Table 8)
- Vital signs (Section 6.3.3)
- 12-lead ECG (in triplicate) (Section 6.3.4.2)
- Review of AEs
- Review of concomitant medications
- C-SSRS (Since Last Update; Appendix D)
- DSS (Section 6.2.1)
- FSS (Section 6.2.2)
- Cogstate Detection Test (Section 6.2.3.1)
- Cogstate Identification Test (Section 6.2.3.2)
- Cogstate One Back Test (Section 6.2.3.3)
- MDHI (Section 6.2.4)
- ESS (Section 6.2.5)
- CGI-S of EDS (Section 6.2.6)
- PGI-S of EDS (Section 6.2.7)
- Review study drug compliance/accountability (Section 5.5 and Section 5.6)

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

7.3.2.4. Visit 8/End-of-Treatment Visit for the Open-Label Extension Phase

Patients are to undergo an EOT Visit (Visit 8) after they complete the study; the evaluations of safety and effectiveness to be performed at the EOT Visit in the OLE Phase are the same as those listed for Visit 7, which is a 6-month on-site study visit (Section 7.3.2.3).

7.3.2.5. Early Termination Visit for the Open-Label Extension Phase

Every effort should be made to perform the ET Visit evaluations for patients who terminate early from the OLE Phase of the study. At the ET Visit, the reason for early termination must be recorded.

The evaluations of safety and effectiveness to be performed at the ET Visit are the same as those listed for Visit 7, which is a 6-month on-site study visit (Section 7.3.2.3).

7.4. Safety Follow-Up Telephone Contacts

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

Patients in the OLE Phase will receive a TC from the study site 15 (±3) days and 30 (+3) days after their final dose of study drug to assess for AEs (including inquiries regarding signs and symptoms of arrhythmia, any other cardiac manifestations [e.g., syncope], and psychiatric events [e.g., suicidality, compulsive behavior, anxiety]) and concomitant medication use.

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

7.5. Unscheduled Visits and Assessments

Unscheduled visits and assessments in the Double-Blind Treatment Phase and OLE Phase of the study may be conducted by telephone or at an on-site study visit and should be performed if clinically indicated in the opinion of the Investigator.

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

- Abbreviated physical examination (Section 6.3.2)
- Vital signs (Section 6.3.3)
- Review of AEs
- Review of concomitant medications
- Review of study drug compliance/accountability (Section 5.5 and Section 5.6)

At a minimum, the following assessments are to be performed at unscheduled visits conducted by telephone:

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

Other assessments (e.g., 12-lead ECGs, clinical laboratory tests, urine pregnancy test, C-SSRS) may be completed based on the reason for the unscheduled visit and at the Investigator's discretion. Unscheduled visits for clinically significant Holter monitoring results require a 12-lead ECG (in triplicate) to be performed as detailed in Section 6.3.4.

8. SAFETY MONITORING AND REPORTING

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

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

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

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

Examples of AEs include:

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

The following examples would not be considered AEs:

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

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

8.1.2. Definition of a Serious Adverse Event

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

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

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

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

8.1.3. Definition of a Suspected Adverse Reaction

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

8.1.4. Definition of a Serious Suspected Adverse Reaction

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

8.1.5. Definition of Unanticipated Problems

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

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

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

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

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

8.2.2. Relationship to Study Drug

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

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

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

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

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of seriousness, severity, or causality will be collected from the time the patient provides written informed consent through 30 (+3) days after final dose of study drug (Safety Follow-up TCs, Section 7.4).

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

8.3.2. Follow-up of Events

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

All AEs and SAEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the patient is lost to follow-up or the patient withdraws consent).

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

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

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

During this study, if the Investigator determines that an event meets the protocol definition of an SAE, regardless of relationship to study drug, he/she must notify the Sponsor **within 24 hours of becoming aware of the SAE**. The SAE report form (completed with all available information) must be sent to the Sponsor via e-mail or facsimile **within 24 hours of the Investigator becoming aware of the SAE**. The Investigator must be diligent about providing additional information as needed. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

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

- AE record
- Medical history
- Prior and concomitant medications

Also, any laboratory test results, diagnostic test results, or medical reports relevant to the SAE should be provided; however, certain patient identifying information (i.e., name, address, and

other identifying information not collected in the patient's eCRF) is to be redacted from copies of the patient's medical records.

In rare circumstances and in the absence of e-mail capacity, a copy of the SAE reporting form may be sent to the Sponsor by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the timeframes outlined.

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

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

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

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

The following information should be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the

appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence can be reported and legal obligations and ethical responsibilities regarding the safety of other patients are met.

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

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

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

8.4.4. Pregnancy Reporting

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

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

9. STATISTICAL CONSIDERATIONS

9.1. General Considerations

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

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

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

9.1.1. Estimand

The primary efficacy endpoint is defined as the change in DSS score from Baseline to Week 11 for pitolisant compared with placebo. The primary comparison of interest will be higher dose pitolisant compared with placebo.

The target population is all patients in the modified intent-to-treat (mITT) population with DM1 as defined by the inclusion/exclusion criteria.

A treatment policy strategy will be utilized to address intercurrent events. Data will be analyzed as reported; no special data handling or imputation will be applied to account for intercurrent events such as use of concomitant medications, halting treatment, or study discontinuation.

The population-level summary will be the least-square means from the primary endpoint model (Section 9.4.2.1.1).

9.1.2. Multiple Comparisons

The DSS will be the primary endpoint measure. All statistical analyses will be purely descriptive.

9.1.3. Missing Data

Every effort will be made to retain patients in the study; however, patients are free to withdraw from the study at any time for any reason. Patients who withdraw early will be asked to return to the clinic for an early termination visit for completion of assessments (Schedule of Assessments, Double-Blind Treatment Phase).

9.2. Determination of Sample Size

[redacted]

9.3. Analysis Populations

The safety analyses will be conducted on the safety population. The mITT population will be used for the primary efficacy analysis. The PK population will be used for PK analyses. Patients will be analyzed according to randomized treatment assignment for efficacy assessments and according to treatment received for safety assessments.

9.3.1. Modified Intent-to-Treat Population

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

9.3.2. Double-Blind Safety Population

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

9.3.3. Open-Label Safety Population

The open-label safety population will include all patients who are enrolled in the OLE Phase and take at least one dose of open-label study drug. Patients will be analyzed according to treatment received in the Double-Blind Treatment Phase (identical to the group they are reported under for the double-blind safety), active arms pooled, and overall.

9.3.4. Pharmacokinetic Population

The PK population will include all patients who received at least one dose of study drug and have calculable concentrations of pitolisant and/or its major metabolite available for analysis.

9.4. Statistical Analysis Methods

9.4.1. Disposition and Demographics

The number and percentage of patients in each analysis population will be summarized. The number of patients screened, and patients enrolled, and the number and percentage of patients completing the Double-Blind Treatment Phase of the study, discontinuing from the Double-Blind Treatment Phase of the study (including reasons for discontinuation), and entering the OLE Phase (with and without completion of the double-blind) will be summarized. All percentages will be calculated using the number of patients enrolled as the denominator.

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

Demographics and baseline characteristics will be reported for the efficacy, double-blind safety, open-label safety, and PK populations. Categorical items will be reported with counts and percentages; continuous items will be reported using summary statistics (mean, SD, median, minimum, maximum). Data will not be re-collected at entry to the OLE Phase but will be reported for the subset of patients that enter the OLE Phase.

9.4.2. Efficacy Analysis

9.4.2.1. Double-Blind Treatment Phase

Double-Blind analyses will be completed once all patients have completed (or discontinued) the Double-Blind Treatment Phase of the study, and the associated data are frozen and unblinding is completed; patients may still be ongoing in the OLE Phase of the study at the time Double-Blind analyses are performed.

9.4.2.1.1. Primary Efficacy Analysis

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the Baseline Visit to Week 11 for each of the treatment groups and for the active groups combined. The change from Baseline will be analyzed with mixed model repeated measures (MMRM). Fixed effects will be included for treatment, baseline value, treatment visit, treatment × visit interaction, and wake-promoting agent stratification factor. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo and the pooled active groups vs placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled estimates will be created via model contrasts.

9.4.2.1.2. Secondary Efficacy Analysis

Analysis of the secondary efficacy endpoints will utilize parallel methodology to that used for the primary efficacy analysis, adjusted as appropriate for distributions and collection time points. Full details will be provided in the SAP.

9.4.2.2. Open-Label Extension Analyses

Summary statistics will be reported for the measures of effectiveness at each visit where it is collected.

9.4.3. Safety Analysis

All safety analyses will be completed for the double-blind safety and open-label safety populations. All safety data will be tabulated or listed. No formal statistics will be performed for the safety analysis.

Adverse events that occur between the time written informed consent is provided and the start of study drug administration will be considered pretreatment AEs. Adverse events that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized. Adverse events leading to study withdrawal, if any, will be listed separately. Adverse events will be summarized with counts and percentages.

Laboratory parameters will be summarized. For each laboratory test, individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline to the lowest and to the highest on study value in and out of the normal range as well as by visit. Laboratory parameters will also be summarized by visit.

The change from Baseline to each visit for vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed. ECG and Holter monitor abnormalities, cardiac arrhythmias and other categorical outcomes will be summarized with counts and percentages. Continuous outcomes will be reported using summary statistics. Results of C-SSRS will be listed.

9.4.4. Pharmacokinetic Analyses

Concentrations of pitolisant and its major metabolite will be assayed using a validated bioanalytical method. Trough and t_{max} (3 hours [±30 minutes] post dose) concentrations will be reported in the CSR. Concentration-time data of pitolisant and BP1.3484 will be summarized using descriptive statistics.

9.5. Interim Analysis

No interim analysis is planned. Results of the Double-Blind Treatment Phase will be reported following database lock once all patients have completed or discontinued the Double-Blind Treatment Phase of the study.

10. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory Authority Approval

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

11.2. Ethical Conduct of the Study

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

11.3. Institutional Review Board/Ethics Committee Approval

The Investigator or the Sponsor is responsible for submitting the following documents to the IRBs/ECs for review and, if applicable, approval: study protocol, ICF, IB, recruitment materials, information about study compensation to patients, and any information provided to potential patients.

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

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

11.4. Informed Consent Process

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

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

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

nontechnical as practical and understandable to the patient. The ICF must provide the patient with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF details the requirements of the participant and the fact that they are free to withdraw at any time without giving a reason and without prejudice to their further medical care. Before informed consent is obtained, the patient should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the patient.

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

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

11.5. Confidentiality

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

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

The patient's contact information will be securely stored at each clinical site for internal use during the study. Throughout the study, a patient's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. Copies of any patient source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., patient name, address, and other identifier fields not collected in the patient's eCRF). At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the IRB and institutional regulations.

To comply with ICH guidelines for cGCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives

from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs to review the patient's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization by the patient as part of the informed consent process (Section 11.4).

12. STUDY ADMINISTRATION

12.1. Clinical Monitoring

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

In the event monitoring of source data by monitors cannot be completed on site due to potential restrictions related to the COVID-19 pandemic, monitoring of source data may be completed remotely.

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

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

12.2. Management of Protocol Amendments and Deviations

12.2.1. Protocol Modification

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

12.2.2. Protocol Violations and Deviations

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

be documented at the site and in the Sponsor files. In the event of an important protocol deviation, the site will notify the Sponsor or designee. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, as required.

12.3. Financial Disclosure

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

12.4. Suspension or Termination of Study or Investigational Site

12.4.1. Suspension of Study

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

12.4.2. Termination of Study or Investigational Site

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

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

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

12.5. Publication and Information Disclosure Policy

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

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

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

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

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

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APPENDIX A. PATIENT SLEEP DIARY FOR SCREENING (EXAMPLE)

Patient ID # _____ Site ID # _____

HBS-101-CL-005 Daily Sleep Diary

Screening Period

- Please complete this log for at least 7 days of Screening.
- Please complete the log every morning upon wakening.
- "Date" is the date when you are filling out the log, which will usually be one day after you went to bed, assuming you went to bed before midnight.
- "What time did you go to bed last night" means the time that the lights were turned off, and you were trying to sleep.
- "What time did you wake up this morning" means the time when you woke up and no longer slept before getting out of bed in the morning.

	What time did you go to bed *last night*?			What time did you wake up *this morning*?		
Date (mm/dd/yy)	Hour	Minute	AM/PM	Hour	Minute	AM/PM

Page **1** of **1**

Patient Initials and Date (initial/date when page is complete):_____
Sleep Diary Version 1, 08Mar2021

APPENDIX B. PATIENT STUDY DRUG DOSING DIARY FOR DOUBLE-BLIND TREATMENT PHASE (EXAMPLE)

Patient ID # _____ Site ID # _____

HBS-101-CL-005 Daily Dosing Diary

Study Drug, Titration Weeks 1-3							
Please record the date and number of tablets taken daily from each bottle.							
Study Drug, Week 1							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 2							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 3							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
DATE of the Day before Visit 3 (mm/dd/yy)			DO NOT TAKE DAILY DOSE OF STUDY DRUG BEFORE ARRIVING AT STUDY SITE FOR VISIT 3				
TIME of dose the Day before Visit 3 AM/PM							

Page **1** of **4**

Patient Initials and Date (initial/date when page is complete):_____
Daily Dosing Diary, V1 08Mar2021

Patient ID # _____ Site ID # _____

HBS-101-CL-005 Daily Dosing Diary

Study Drug, Weeks 4-7							
Please record the date and number of tablets taken daily from each bottle.							
Study Drug, Week 4							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 5							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 6							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 7							
Date (mm/dd/yy)							
Bottle A							
Bottle B							

Patient Initials and Date (initial/date when page is complete):_____

Daily Dosing Diary, V1 08Mar2021

Patient ID # _____ Site ID # _____

HBS-101-CL-005 Daily Dosing Diary

Study Drug, Week 8							
Please record the date and number of tablets taken daily from each bottle.							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 9							
Please record the date and number of tablets taken daily from each bottle.							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 10							
Please record the date and number of tablets taken daily from each bottle.							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Study Drug, Week 11							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
DATE of the Day before Visit 5 (mm/dd/yy)			**DO NOT TAKE DAILY DOSE OF STUDY DRUG BEFORE ARRIVING AT STUDY SITE FOR VISIT 5**				
TIME of dose the Day before Visit 5 AM/PM							

Patient Initials and Date (initial/date when page is complete):_____
Daily Dosing Diary, V1 08Mar2021

Patient ID # _____ Site ID # _____

HBS-101-CL-005 Daily Dosing Diary

THIS PAGE IS TO BE USED FOR ADDITIONAL ENTRIES, IF NEEDED.

Study Drug							
Please record the date and number of tablets taken daily from each bottle.							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Date (mm/dd/yy)							
Bottle A							
Bottle B							
Date (mm/dd/yy)							
Bottle A							
Bottle B							

Patient Initials and Date (initial/date when page is complete):_____

Daily Dosing Diary, V1 08Mar2021

APPENDIX C. COLUMBIA-SUICIDE SEVERITY RATING SCALE-LIFETIME RECENT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

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

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.
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). Ask about time he/she was feeling the most suicidal.

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)*	**Lifetime**
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** ☐ ☐

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* _____

APPENDIX D. COLUMBIA-SUICIDE SEVERITY RATING SCALE-SINCE LAST CONTACT

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

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

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

Most Severe

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

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

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

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

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

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

APPENDIX E. EXAMPLES OF STRONG CYP2D6 INHIBITORS, STRONG CYP3A4 INDUCERS, MEDICATIONS THAT PROLONG QT INTERVAL, AND CENTRALLY ACTING H_1R ANTAGONISTS

Medication Type	Examples
Strong CYP2D6 inhibitors	paroxetine, fluoxetine, bupropion, quinidine, terbinafine
Strong CYP3A4 inducers	rifampin, carbamazepine, phenytoin, apalutamide, St John's wort, enzalutamide, mitotane
Medications that prolong QT Interval	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide Class 3 antiarrhythmics: amiodarone, sotalol, dofetilide Antipsychotics: ziprasidone, chlorpromazine, thioridazine, haloperidol Antibiotics: moxifloxacin, ciprofloxacin, erythromycin, ketoconazole
Centrally acting H_1R antagonists (sedating or lipophilic H_1R antagonists)	pheniramine maleate, diphenhydramine, promethazine (anti-histamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)

CYP = cytochrome P450; H_1R = histamine 1 receptor

APPENDIX F. DAYTIME SLEEPINESS SCALE (DSS)

DAYTIME SLEEPINESS SCALE

For each statement, circle the number that best corresponds to what you are currently experiencing.

	Never or almost never	Sometimes	Often	Always or almost always
1. I take one or more naps during the day.	0	1	2	3
2. I occasionally have a sudden urge to sleep during the day.	0	1	2	3
3. I occasionally fall asleep in front of the television or at the movies.	0	1	2	3
4. I have difficulty remaining still for long periods of time.	0	1	2	3
	Always or almost always	Often	Sometimes	Never or almost never
5. I am generally in great shape during the day.	0	1	2	3

Please note that question #5 is scored in the reverse order.

Total Score: _____

Daytime Sleepiness Scale
Version date 12Nov2021

APPENDIX G. FATIGUE SEVERITY SCALE (FSS)

Fatigue Severity Scale

Below are a series of statements regarding your fatigue. By fatigue we mean a sense of tiredness, lack of energy or total body give-out. Please read each statement and choose a number from 1 to 7, where # 1 indicates you completely disagree with the statement and # 7 indicates you completely agree. Please answer these questions as they apply to the past **TWO WEEKS**.

	Completely Disagree						Completely Agree
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my 3 most disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life	1	2	3	4	5	6	7

FSS - United States/English - Mapi Institute.
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APPENDIX H. MYOTONIC DYSTROPHY HEALTH INDEX (MDHI)

THE MYOTONIC DYSTROPHY HEALTH INDEX

(MDHI)

Date: Study:
Initials:
Visit #: Participant #:

THE MYOTONIC DYSTROPHY HEALTH INDEX

Directions: Please check the box that applies to you for each item.

1. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Limitations with your mobility or walking						
b.) Problems with your hands or arms						
c.) Inability to do activities						
d.) Fatigue						
e.) Pain						
f.) Gastrointestinal issues						
g.) Problems with your vision						
h.) Communication difficulties						
i.) Impaired sleep or daytime sleepiness						
j.) Emotional issues						
k.) Difficulty thinking						
l.) Decreased satisfaction in social situations						
m.) Decreased performance in social situations						
n.) Myotonia						
o.) Breathing difficulties						
p.) Choking or swallowing issues						
q.) Hearing difficulties						

2. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Difficulty staying in a standing position						
b.) Difficulty walking long distances						
c.) Difficulty with stairs						
d.) Inability to walk fast						
e.) Difficulty with balance						
f.) Impaired walking						
g.) Difficulty rising from a seated position						
h.) Inability to run						
i.) Ankle weakness						
j.) Tripping						
k.) Falls						
l.) Difficulty getting up from a lying position						

3. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Hand weakness						
b.) Difficulty doing things with your hands						
c.) Difficulty lifting objects						
d.) Difficulty picking things up with your fingers						
e.) Arm weakness						
f.) Problems reaching things over your head						
g.) Droopy eyelids						
h.) Facial weakness						
i.) Neck weakness						
j.) Impaired ability to open doors or drawers						

4. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Difficulty opening jars or bottles						
b.) Difficulty playing sports						
c.) Trouble going up step ladders						
d.) The inability to keep pace with friends while walking						
e.) Impaired dancing						
f.) Impaired ability to exercise						
g.) Difficulty using a hammer or other tool						
h.) Taking longer to do household chores						
i.) Impaired sexual function						
j.) Problems using buttons or zippers						
k.) Difficulty scrubbing surfaces						
l.) Difficulty cleaning a home						
m.) A change in your activities because of gastrointestinal symptoms						

5. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Poor handwriting						
b.) Slurring of your speech						
c.) Impaired facial expression						
d.) Difficulty communicating with others						
e.) Quiet voice						
f.) Tongue cramping						

6. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Inability to do things that you used to do						
b.) Self-conscious of muscle loss						
c.) Perceived burden to family members						
d.) Increased family stress						
e.) Dissatisfaction with social interactions						

7. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) The reliance on family members						
b.) Decreased independence						
c.) Inability to care for family members						
d.) The avoidance of social situations						
e.) Impaired social interactions						
f.) Difficulty with relationships						

8. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Decreased energy						
b.) Impaired endurance						
c.) Tired muscles						

9. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Back pain						
b.) Muscle stiffness						
c.) Leg pain						
d.) Limited activity from pain						
e.) Muscle cramping						
f.) Pain all over						
g.) Arm pain						

10. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Hand myotonia						
b.) Myotonia all over						
c.) Jaw stiffness (myotonia)						

11. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a) Diarrhea						
b.) Constipation						
c.) Gas						
d.) Abdominal pain						
e.) Stomach cramping						

12. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Problems swallowing						
b.) Fear of choking						

13. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Poor night vision						
b.) Visual loss						
c.) Eye irritation						

Please Continue ⟶

14. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Frustration						
b.) Reduced enjoyment with activities						
c.) Fear of injury with activity						
d.) Depression						
e.) Damaged pride with loss of independence						
f.) Feeling overwhelmed						
g.) Moodiness						
h.) Increased stress						
i.) Anxiety						
j.) Impaired self-image						
k.) Anger						

15. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Daytime sleepiness						
b.) Excessive sleep requirements						
c.) Difficulty falling asleep at night						

16. How much does the following impact your life now?	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
a.) Decreased motivation						
b.) Fear of a worsening ability to think						
c.) Thinking fatigue						
d.) Decreased ability to think fast						
e.) Memory problems						
f.) Disorganization						
g.) Problems concentrating						
h.) Difficulty with comprehension						

END OF SURVEY

APPENDIX I. EPWORTH SLEEPINESS SCALE (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

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

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

This refers to your usual way of life recently.

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

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

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

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

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

THANK YOU FOR YOUR COOPERATION

ESS - United States/English - Version of 19 Jan 18 - Mapi.
ID037309 / ESS_AU1.0_eng-US2.doc

APPENDIX J. CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGI-S) FOR EXCESSIVE DAYTIME SLEEPINESS

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

[redacted]