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

SAP Date (last revision date): November 3, 2023

Statistical Analysis Plan (SAP)

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 Version No./Date:	Protocol Amendment 5 / 18Jul2023
CRF Version No./Date:	Version 4.0 / 09May2023
SAP Version No./Date:	Version 3.0 / 03Nov2023

1 Approvals

Sponsor	
Sponsor Name:	Harmony Biosciences, LLC
Representative/ Title:	[redacted]
Signature /Date:	
ICON	
Biostatistician / Title:	[redacted]
Signature /Date:	

2 Change History

The table below details changes from the prior approved version of the statistical analysis plan (SAP).

Version/Date	Change Log
1.0 / 27-Apr-2021	Created as new
2.0 /03Nov2023	**Section 6.0:** Updated the protocol version and the change of CRO name. **Section 6.1:** Added justification to indicate that treatment is summarized by total treatment in the Open-Label Extension Phase of the study. **Section 8.1:** Updated the section to match changes in the protocol to the duration of (i.e. to define the end of the Open-Label Extension Phase of the study). **Section 8.2:** • Removed sample size and statistical power estimation. • Updated the section to match changes in the protocol to the sample size considerations. **Section 8.3**: Added stratification factor in the randomization. **Section 9.1**: • Updated the section to match changes in the protocol to the primary efficacy endpoint. • Removed Z-score (aggregation of Daytime Sleepiness Scale [DSS] and Mean Sleep Latency [MSL]) endpoint **Section 9.2.1**: • Updated visit window in the Double-Blind Treatment Phase to be identical across assessments. • Updated visit window schedule for the Open-Label Extension Phase (last visit is now visit 8 / Month 15). • Updated Visit label to include the visit number and study day/month. • Added rules for revising study day, if there is a re-start in dose escalation in the Double-Blind Treatment Phase. **Section 10.0:** Clarified the analysis population and treatment group for the Open-Label Extension Phase. **Section 10.3:** Updated details on how the patients will be summarized. **Section 10.4:** Revised PK population definition to match the protocol. **Section 10.5:** Removed Maintenance of Wakefulness Test (MWT) population **Section 11.0:** Updated the section to match changes in the protocol. **Section 11.1.1:** Revised to add screen failure details and patient disposition with respect to treatment and study during the Open-Label Extension Phase. **Section 11.1.2:** Clarified summary for Double-Blind Treatment Phase and overall for the OLE Phase. **Section 11.1.3:** Clarified that the failed inclusion/exclusion criteria for randomized patients will be listed. **Section 11.2.3:** Removed summary for the seizure history, as it is not required. **Section 11.3.3**: New added section to provide details on identifying wake-promoting agents. **Section 11.4:** Clarified that wake-promoting agents at randomization will also be derived from the database. Added stratification factor to inferential model. In addition, minor reorganization to section numbering to accommodate revisions to match changes in the protocol. **Section 11.4.1**:

	• Updated the section to match changes in the protocol. • Replaced Analysis of Covariance (ANCOVA) with Mixed Model Repeated Measures (MMRM) for primary endpoint analysis method **Section 11.4.1.1**: Updated pooling strategy to clarify the pooled active groups. **Section 11.4.3:** Removed analysis of site effect in statistical models for study endpoint analysis. **Section 11.4.3.1.2:** Removed multiple imputation (MI) and sensitivity analyses **Section 11.6.1:** Included summary by system organ and class and preferred term for all adverse events and all serious adverse events. **Section 11.6.3:** Added details on imputation of results reported as “<xx” or “>xx”. **Section 11.6.4:** Added vital sign reference ranges and shift table summary. Removed abnormal criteria and associated summary. **Appendix 4**: Added stratification factor in SAS code examples.

3 Table of Contents

4 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the analyses and reporting of data collected under Harmony Biosciences, LLC, Protocol HBS-101-CL-005.

5 Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Endpoints
- Applicable Study Definitions
- Statistical Methods

6 Introduction

This SAP should be read in conjunction with the study protocol Amendment 5 dated 18 July 2023 and electronic case report form (eCRF) v4.0 dated 09May2023. Any changes to the protocol or eCRF may necessitate updates to the SAP.

The SAP Version 1 was approved on 28 April 2021. This SAP Amendment 1 (Version 2.0) will include changes to the protocol through protocol Amendment 5. Final approval of the SAP by Harmony Biosciences, LLC and ICON will occur prior to the database entry lock and unblinding of the database for the analyses of the Double-Blind Treatment Phase of the study.

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.

6.1 Changes from Protocol

The Intent-to-Treat Population referenced in protocol Amendment 4 is referred to as the modified Intent-to-Treat Population (mITT) in the SAP; the definition remains same.

For the Open-Label Extension (OLE) Phase reporting, all patients will be analyzed as a single group, which will be labelled “Total”. All patients will be titrated during a 3-week Titration Period to a dose of 35.6 mg pitolisant (or a maximum dose up to 35.6 mg based on Investigator assessment of tolerability). Additional changes from protocol Amendment 4 include:

- Removed sample size and statistical power calculation
- Removed Z-score (aggregation of Daytime Sleepiness Scale [DSS] and Mean Sleep Latency [MSL]) endpoint
- Removed Maintenance of Wakefulness Test (MWT) population
- Replaced Analysis of Covariance (ANCOVA) with Mixed Model Repeated Measures (MMRM) for primary endpoint analysis method
- Removed analysis of site effect in statistical models for study endpoint analysis
- Removed multiple imputation (MI) and sensitivity analyses

7 Study Objectives

7.1 Primary Objectives

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.

7.2 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)

8 Study Design

8.1 General Design

This is a 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 1). 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 2). 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.

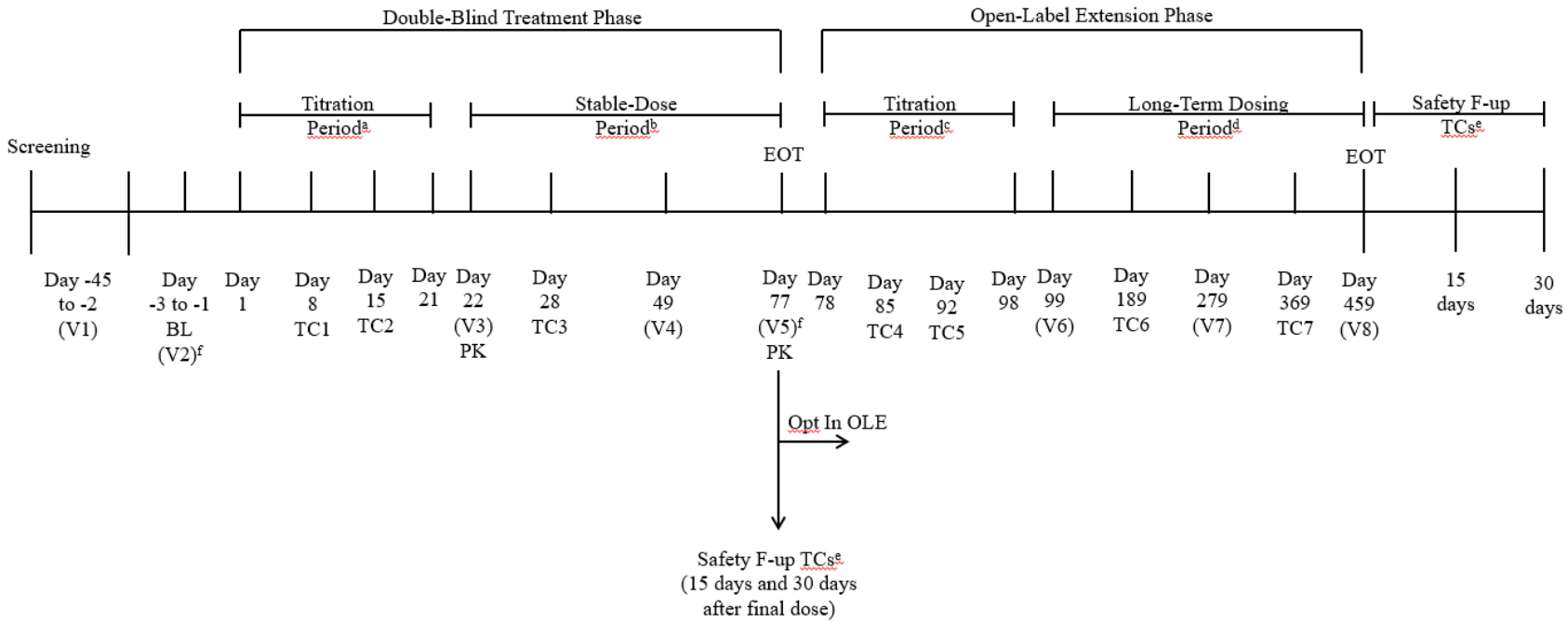
The COVID-19 (Coronavirus Disease 2019) pandemic has had a major impact on the conduct of clinical trials worldwide, including restrictions on travel, dislocation of clinical trial subjects, and the need of many health care facilities to handle an influx of patients with COVID-19. Recognizing the impact of COVID-19 on clinical trials, the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) released guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity

for the duration of the COVID-19 public health emergency. Details of analyses of data collected regarding the impact of COVID-19 on this study are included within the applicable sections.

8.2 Study and Patient Completion

- Patients who completed the DBT Phase are patients who completed treatment during the DBT Phase and entered the OLE Phase and or patients who completed treatment during the DBT Phase and did not enter in the OLE Phase.
- Patients who completed the study drug who discontinued study drug during the DBT Phase and continued to meet the eligibility criteria for the study.

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 1); 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, Protocol 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.

Table 1: Study Drug Dosing in the Double-Blind Treatment Phase

Treatment Groups	Titration Period (3 Weeks)			Stable Dose Period (8 Weeks)
	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.

Table 2: Pitolisant Dosing in the OLE 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 (Protocol 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.

8.3 Sample Size Considerations

[redacted]

8.4 Randomization

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 via an interactive response technology (IRT) to lower dose pitolisant, higher dose pitolisant, or matching placebo. The randomization will be stratified by concomitant use of wake-promoting agents (Yes/No).

Enrolled patients will be allocated a unique identification number in a sequential order; blocks will be dynamically assigned to each stratification level to balance the randomization within each stratification level. Following randomization, Harmony Biosciences will provide all study drug in a packed and labelled kit, and the IRT will identify the kit number to be dispensed to the patient according to the treatment assigned in the randomization schedule.

9 Study Endpoints, Conventions and Derivations

9.1 Endpoints

Table 3 and Table 4 list the objectives and the assessments being used for the respective endpoints in the study.

Table 3: Double-Blind Treatment Phase Objectives and Endpoints

DOUBLE-BLIND TREATMENT PHASE	
Primary Objective	**Primary Endpoint**
To evaluate the safety and efficacy of pitolisant compared with placebo in treating EDS in patients with DM1.	The change in Daytime Sleepiness Scale (DSS) score from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo.
Secondary Objectives	**Secondary Endpoints**
To assess the impact of pitolisant on fatigue in patients with DM1.	The change in Fatigue Severity Scale (FSS) score from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo.
To assess the impact of pitolisant on selected domains of cognitive function in patients with DM1.	The change from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo assessment of Cogstate Computerized Cognitive Battery Tests in: • Identification (Attention), SART (attention), Detection (Psychomotor Function), and One Back (Working Memory).
To assess the impact of pitolisant on EDS in patients with DM1.	The change in Epworth Sleepiness Scale (ESS) score from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo.
To assess investigator and patient impression of overall impact of pitolisant on burden of disease in patients with DM1.	The change in score from Baseline to Week 11 (Visit 5) for pitolisant compared with placebo in: • Clinical Global Impression of Severity (CGI-S) for EDS • Patient Global Impression of Severity (PGI-S) for EDS • Myotonic Dystrophy Health Index (MDHI)
Exploratory Objectives	**Exploratory Endpoints**
To assess the impact of pitolisant on EDS in patients with DM1.	• The change in MSL based on MWT from Baseline to Week 11 for pitolisant compared with placebo.
Safety	**Safety Endpoints**
To assess the safety and tolerability of pitolisant	• Adverse Events (AEs) • Clinical laboratory test results • Vital signs • 12-lead electrocardiogram (ECG) • Holter monitoring • C-SSRS assessment • Physical examinations

Abbreviations: 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; EDS = Excessive Daytime Sleepiness; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MDHI = Myotonic Dystrophy Health Index; MSL = Mean Sleep Latency; MWT = Maintenance of Wakefulness Test.; PGI-S = Patient Global Impression of Severity; SART = Sustained Attention to Response Task

Table 4: Open-Label Extension Phase Objectives and Endpoints

OPEN LABEL EXTENSION PHASE	
Objectives	**Efficacy Endpoints**
To assess effectiveness of pitolisant during long-term treatment (during the OLE Phase).	• Changes from Baseline in: ○ DSS ○ ESS ○ FSS ○ Cogstate Detection Test, Cogstate SART, Cogstate Identification Test, and Cogstate One Back Test ○ MDHI ○ CGI-S of EDS ○ PGI-S of EDS
Safety	**Safety Endpoints**
To assess the safety and tolerability of pitolisant	○ AEs ○ Clinical labs ○ Vital signs ○ 12-lead ECG ○ Holter monitoring ○ Suicidality ○ Physical examinations

Abbreviations: AE = Adverse Event; CGI-S = Clinical Global Impression of Severity; DSS = Daytime Sleepiness Scale; ECG = Electrocardiogram; EDS = Excessive Daytime Sleepiness; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MDHI = Myotonic Dystrophy Health Index; OLE = Open-Label Extension; PGI-S = Patient Global Impression of Severity, SART = Sustained Attention to Response Task.

9.2 Study Day Windows

For each patient there will be a screening period, a Double-Blind Treatment Phase, and an optional OLE Phase.

The study day for data collected after the first dose of study drug will be calculated as visit/assessment date – first dose date + 1. For data collected prior to first dose, the study day will be calculated as visit/assessment date – first dose date. The first dose date refers to the date the study drug was taken for the first time, i.e., at the beginning of the Double-Blind Treatment Phase.

9.2.1 Visit Window

The visit window and pharmacokinetic (PK) draw window appear in Table 5 and Table 6, respectively. Unless otherwise stated the endpoints will be analyzed and reported using the analysis visits.

Analysis visit windows will be derived for the Double-Blind Treatment Phase and used for the analyses. For C-SSRS, no analysis window will be applied; data will be reported using the nominal visit. No summary will be created for C-SSRS data, which will be included in a listing only. Therefore, no analysis windowing will be applied on C-SSRS data.

During the Double-Blind Treatment Phase, if a patient stopped taking treatment in the first week of the study (i.e., stopped treatment within 7 days of the date of first dose) for a reason other than an adverse event and then re-started study treatment more than 14 days after the treatment interruption, the analysis visit window

for post-baseline visits will be derived using the date the patient re-started their study treatment (i.e., the visit window will not be based on date of first dose for that patient).

For the OLE Phase, nominal visit will be used.

Table 5: Analysis Visit Window and Target Day

Phase	Protocol Visit	Analysis Visit	Target Day	Analysis Visit Window Lower Limit	Analysis Visit Window Upper Limit
Screening	Visit 1	Baseline	-1	- inf	1
	Visit 2				
Double-Blind	Visit 3	Visit 3 (Day 22)	22	2	35
	Visit 4	Visit 4 (Day 49)	49	36	63
	Visit 5	Visit 5 (Day 77)	77	64	Treatment Phase Completion[a]
OLE	Visit 6	Visit 6 (Day 99)	99	maximum of (92, Treatment Phase Completion)	129
	Visit 7	Visit 7 (Month 9)	279	130	309
	Visit 8	Visit 8 (Month 15)	459	310	489

Abbreviations: OLE = Open-Label Extension.
[a]In the Double-Blind Treatment Phase, if the patient did not enter the OLE Phase, the upper limit of the visit window should be the date of the end of the completion of the treatment phase as collection in the CRF; if the patient entered the OLE Phase, the upper limit of the visit window should be the first dose of study drug intake in the OLE.

Table 6: PK Draw Timing

Phase	Visit	Target Day	Timepoints
Double-Blind	Visit 3	Day 22	• Pre-dose • 3 hours (±30 minutes) post-dose
	Visit 5	Day 77	• Pre-dose • 3 hours (±30 minutes) post-dose

9.2.2 Data Selection for Multiple Results

Double-Blind Treatment Phase: For post-baseline assessments, if there are multiple non-missing results within the same analysis window (including scheduled and unscheduled results), then the non-missing result that is closest to the target date will be used in the analyses; if more than one result is equally close, the result that is after the target date of the assessment will be used. If necessary, time of the assessment (if collected) will be used to determine the record to be selected.

OLE Phase: Assessments performed at nominal visits will be used in the analyses/summaries. Unscheduled assessments will only be used to determine worst, lowest and/or highest results post-baseline where applicable.

Twelve-lead ECGs will be collected in triplicate at each nominal visit as prespecified in the protocol. The mean value of the triplicate (or duplicate) at each nominal visit will be derived. The rules defined above for the post-baseline assessments and for the baseline (section 9.3) will be applied to determine which mean values will be summarized. For the overall interpretation, the worst interpretation across the triplicate (or duplicate) for each given nominal visit will be selected first, and then the rules defined above for the post-baseline assessments and for the baseline (section 9.3) will be applied to determine the results to be summarized.

9.3 Baseline

For the Double-Blind Treatment Phase, Baseline is defined as the last non-missing record or measure collected prior to the study drug administration. For the OLE phase, Baseline will be identical to the Double-Blind Treatment Phase (i.e., the last non-missing record or measure collected prior to study drug administration).

9.4 Double-Blind and OLE Analyses Reporting

The data collected for the Double-Blind Treatment Phase and the OLE Phase are included in the same database.

A data cut will be performed at the end of the Double-Blind Treatment Phase and another one will be performed at the end of the OLE Phase. The date of first dose in the OLE Phase will be used to determine if a patient entered the OLE Phase. A data cut-off will be applied to the datasets and only data related to the Double-Blind Treatment Phase will be reported:

- Baseline and baseline characteristics.
- Visits performed in the Double-Blind Treatment Phase, up to and including Visit 5 (Week 11) for patients who entered the OLE Phase, and up to the safety follow-up visits for patients who opt out of the OLE Phase.
- For patients who entered the OLE Phase, any adverse event (AE) or medication that started up to and including the last dose of study drug in the Double-Blind Treatment Phase. For this patient group a (any AE or medication that started after and up to 30 days after the last dose of study drug in the Double-Blind Treatment Phase will be reported in separate listings, i.e., they will be excluded from the Double-Blind Treatment Phase summary tables).
- For patients who opt out of the OLE Phase, all AEs and medications reported through the final 30-day safety follow-up telephone contact will be reported as part of the Double-Blind Treatment Phase.

The date of first dose in the OLE Phase will be kept in the datasets to determine if the patient has entered the OLE Phase.

OLE Phase:

For reporting the OLE analyses, no data cut-off will be applied to the datasets. Only data related to the OLE Phase will be reported:

- Demographics and baseline characteristics for patients who received at least one dose of study drug within the OLE Phase
- Baseline safety and efficacy data (section 9.3)
- Safety and efficacy reported during the OLE Phase
- AEs and concomitant medications started on or after the 1st dose of OLE study drug intake

10 Analysis Sets

For the Double-Blind Treatment Phase: Safety analyses will be conducted for 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 their randomized treatment for efficacy assessments and according to the actual treatment received for safety assessments.

For the OLE Phase: The open-label safety population will be used.

10.1 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 during the Double-Blind Treatment Phase. This population will be used to summarize the primary, secondary, and other efficacy data. Patients will be analyzed according to their randomized treatment.

10.2 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 their treatment received. In the case of mis-dosing, patients will be counted at the highest dose they received in the Double-Blind Treatment Phase.

10.3 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.

10.4 Pharmacokinetic Population

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

11 Statistical Methods

All analyses will use SAS version 9.4 or higher.

Categorical variables will be summarized using counts and percentages based on the specified population total. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous data will be summarized using non-missing observations (n, mean, SD, median, minimum, and maximum). The minimum and maximum values will be displayed to the same level of precision as the raw value. Mean, and median will be rounded to 1 decimal place greater than precision of the original value. The SD will be rounded to 2 decimal places greater than precision of the original value. Confidence intervals (CI), least squares (LS) means, and standard error (SE) will be provided as appropriate. CIs, LS means will be presented with a precision similar to mean and SEs will be presented with a precision similar to SD.

This is an exploratory study. Except for the analysis of the SART endpoint (using Kruskal Wallis test and for which the p-value will be reported), no formal statistical hypothesis testing (including the generation of p-values) is planned for other study endpoints. For these endpoints, the p-values will be included in supporting statistical appendix.

All listings will be displayed by treatment arm (where applicable), patient identifier and date of assessment. Age, sex, and race will be presented.

11.1 Patient Disposition

11.1.1 Disposition

For the Double-Blind Treatment Phase, the number and percentage of patients screened, enrolled, completing the Double-Blind Treatment Phase, discontinuing from the Double-Blind Treatment Phase, and enrolled in OLE will be summarized, together with a breakdown of the corresponding reasons for withdrawal from study drug and from the study. Also, the number and percentage of patients included in each analysis set will be summarized.

The number of patients who screen failed and the reason for screen failure will be tabulated. A supportive data listing will be provided for the screen failure patients and will include the reason for screen failure and the list of inclusion/exclusion criteria failed.

For the OLE Phase, the number and percentage of patients enrolled in the OLE Phase, completing the OLE Phase, discontinuing treatment and/or from the OLE Phase and the reasons for discontinuation from the treatment and/or the OLE Phase will be summarized.

Patient disposition data will be presented in a data listing for Double-Blind safety and open-label safety populations.

11.1.2 Important Protocol Deviations

The number and percentage of patients with important protocol deviations (PD) by category will be summarized by treatment arm, active arms pooled, and overall for the Double-Blind Treatment Phase and total for the OLE Phase.

Important PDs will be listed. All COVID-19 related PDs will be listed separately.

11.1.3 Inclusion and Exclusion Criteria

Failed inclusion and exclusion criteria for the randomized patients will be presented in a data listing.

11.2 Demographic and Baseline Characteristics

11.2.1 Demographics

Baseline data will be summarized for continuous and categorical variables as applicable.

The following demographic and baseline characteristics will be summarized:

- Sex (female, male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Age (years), as continuous variable
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index at baseline (kg/m2) defined as Weight (kg)/[Height (m)]2
- Women of child-bearing potential

At the time of the Double-Blind Treatment Phase database entry lock, the above information will be tabulated by treatment arm and overall using the mITT and the Double-Blind safety populations. At the time of OLE Phase database lock, the above information will be tabulated by using the OLE Safety Population.

Data will not be re-collected at entry to the OLE Phase but will be reported for the subset of patients who enter the OLE Phase.

Demographic information will be presented in a data listing. No statistical testing will be performed on the demographic data.

11.2.2 Medical History

A complete medical history will be obtained at Screening to ensure patients qualify for the study and will be updated at the Baseline Visit if needed.

Medical history will be summarized by treatment arm for all patients in the safety population. Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); the version used will

be included in the tables and listings footnotes and summarized by system organ class and preferred term. Medical history data will be presented in a data listing.

11.2.3 Seizure History

Seizure history will be obtained at Screening and will be updated at the Baseline Visit if needed.

For patients in the safety population, in those patients with a history of a seizure disorder, the following aspects of their seizure history will be summarized.

- Total number of patients with a history of seizure disorder
- Whether there has been any change in seizure activity in the past 3 months (prior to the study)
- Type of seizure disorder
- Average weekly seizure frequency
- Average seizure duration in seconds

Seizure history data will be presented in a data listing.

11.2.4 Myotonic Dystrophy Type 1 History

Confirmation of a patient's diagnosis of DM1 will be obtained via review of the patient's medical records and genetic testing will be performed during Screening to confirm cytosine-thymine-guanine (CTG) repeat of ≥100. Number of repeats will be summarized and listed. Age at diagnosis of DM1 will be tabulated.

Age at diagnosis of DM1 (years) = (date of diagnosis – date of birth)/365.25

The date of diagnosis of DM1 will be presented in the baseline characteristics listing.

11.3 Treatments

11.3.1 Prior, Concomitant and Prohibited Medications

Medications stopped prior to the first dose of study drug will be classified as prior medication. Medications started with or after the first dose of study drug will be classified as concomitant. Medications started before the first dose of study drug and stopped after the first dose of study drug will be classified as both prior and concomitant.

Medications will be categorized by medication group and subgroup according to World Health Organization (WHO) drug dictionary (the version used will be included in the tables and listings footnotes). Refer to the Coding Conventions document for this study.

Missing or partial medication start/stop date will be imputed as described in Appendix 2. A conservative approach will be used when flagging medications.

Prior, concomitant, and prohibited medications will be summarized for the safety populations. All medications will be listed.

11.3.2 Prohibited and Restricted Concomitant Medications

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

Use of opiates is not permitted in the study.

Use of strong cytochrome P450 (CYP) 2D6 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 (examples are listed in Appendix 3) are allowed during the OLE Phase of the study, but adjustments to the dose of pitolisant is required.

Pitolisant increases the levels of histamine in the brain; therefore, centrally acting H_1R (histamine 1 receptor) 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.

Prohibited medications taken in the study will be reported and summarized with the protocol deviations.

Prior and concomitant medications will be summarized based on the number and percentage of patients using each medication along with the number and percentage of patients using at least one medication within each medication group and subgroup.

For patients who opt to continue in the OLE Phase of the study, only medications started on or before the last dose in the Double-Blind Treatment Phase will be included in the summaries for the Double-Blind Treatment Phase. Medications started after the last dose and up to 30 days after the last dose of treatment in the Double-Blind Treatment Phase will be included in a separate listing in the Double-Blind Treatment Phase and also summarized in the OLE Phase.

11.3.3 Wake-Promoting Agents

Randomization is stratified by concomitant use of wake-promoting agents (Yes/No). 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

The EDC stratification is based on review of these medications prior to randomization (i.e., to identify patients who were taking wake-promoting agents).

The identification of patients who were on wake-promoting agents at the time of randomization, based on review of the medications collected in EDC, will be done prior to database lock and study unblinding for the Double-Blind Phase.

The medical monitor will review the list of medications prior to unblinding of the study for the Double-Blind Treatment Phase to finalize a list of medications considered wake-promoting agents. The finalized list will be used to determine if the patients were taking wake-promoting agents at the time of randomization.

If the start and/or stop dates are partial/missing, the imputations rules defined in Appendix 2 will be used to determine if the medication was taken at the time of the first dose of study drug. If it is not possible to determine if the medication was taken at the time of the first dose of study drug, it will be assumed that the medication was not concomitant.

Number (%) of patients on a wake-promoting agents will be tabulated and summarized.

11.3.4 Extent of Study Drug Exposure

The descriptive statistics will be provided by treatment group for the Double-Blind Treatment Phase analyses and by treatment group received during the Double-Blind Treatment Phase and total for the OLE Phase analyses.

11.3.4.1 Double-Blind Treatment Phase

The duration of exposure to study drug, number of days dose is taken and compliance (during the stable dose period) with study drug dosing will be summarized for the Double-Blind safety population. In addition, the number of tablets taken (i.e., returned - dispensed) will be listed for the titration phase and the stable dose phase in the Double-Blind Treatment Phase.

Study drug accountability including bottle number and number of dispensed and returned tablets will be listed. Study drug not returned will be assumed to have been taken.

Percentage of patients meeting study drug compliance during the stable-dose period will be summarized in the following categories: <80%, ≥80% to ≤120%, and >120%. Major non-compliance is defined as compliance <80% or compliance >120%.

Duration of exposure: Date of last dose in the Double-Blind Treatment Phase – date of first dose in the Double-Blind Treatment Phase + 1.

Number of days with at least one dose (tablet) taken: Duration of exposure in the Double-Blind Treatment Phase – number of days with missed doses in the Double-Blind Treatment Phase.

Study Drug Compliance (stable-dose period): The start date of the stable dose period is the date of Visit 3 (Day 22), and the end of the stable dose period is the last dose date in the Double-Blind Treatment Phase; during that period each patient should take 2 tablets each morning; i.e., compliance is the number of tablets taken during that period (i.e., sum of the tablets dispensed minus the sum of the tablets returned) divided by (2 times the number of days in the period [date of last dose – dispensed date at Visit 3 + 1]).

11.3.4.2 OLE Phase

The duration of exposure to study drug will be summarized for the OLE safety population. Study drug accountability and number of dispensed and returned tablets will be listed.

Duration of exposure: Date of last dose in the OLE Phase – date of first dose in the OLE Phase + 1,

In addition, the following measures of changes in planned dose will be summarized for the OLE safety population:

- Planned average daily dose: sum of the daily dose x for the duration of intake divided by the duration (end date minus start date + 1) of exposure;
- Number and percentage of patients with at least one dose adjustment per reason (AE, dosing error, rechallenge, insufficient effectiveness, change in dose assignment criteria and other);
- Number and percentage of patients with one dose adjustment, with 2 dose adjustments and with > 2 dose adjustments due to any reason;
- Number and percentage of patients with one dose adjustment, with 2 dose adjustments and with > 2 dose adjustments due to AE;
- Number and percentage of patients with one dose adjustment, with 2 dose adjustments and with > 2 dose adjustments due to rechallenge;
- Number and percentage of patients with one dose adjustment, with 2 dose adjustments and with > 2 dose adjustments due to insufficient effectiveness.

11.4 Efficacy Analyses

For the inferential analysis, the stratification factor of wake-promoting agents (Yes/No) will be based on the stratification factor derived in the EDC. If there is more than 10% difference between the stratification factor recorded in IRT versus the stratification factor derived from the prior and concomitant in the EDC(see section 11.3.3), the primary analysis will be repeated using the stratification factor reported in the IRT.

11.4.1 Double-Blind Treatment Phase

All efficacy analyses will be performed on the mITT Population. The analysis approaches for the efficacy endpoints at Visit 5 are detailed in Table 7. Similar analyses (where applicable) for efficacy endpoints collected at Visit 4 will be conducted as well.

Table 7: Double-Blind Inferential Analyses Strategy

Endpoint	Primary/ Secondary/ Exploratory	Inference model	Comparisons of interest
CFB in DSS score at Week 11 (Visit 5)	Primary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in ESS score at Week 11 (Visit 5)	Secondary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in FSS score at Week 11 (Visit 5)	Secondary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in Cogstate Detection Test score at Week 11 (Visit 5)	Secondary	ANCOVA	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in Cogstate Identification Test score at Week 11 (Visit 5)	Secondary	ANCOVA	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in Cogstate One Back Test score at Week 11 (Visit 5)	Secondary	ANCOVA	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in MDHI total Score at Week 11 (Visit 5)	Secondary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in CGI-S score at Week 11 (Visit 5)	Secondary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in PGI-S score at Week 11 (Visit 5)	Secondary	MMRM	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in SART go score at Week 11 (Visit 5)	Secondary	Kruskal-Wallis	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in SART no-go score at Week 11 (Visit 5)	Secondary	Kruskal-Wallis	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo
CFB in SART total score at Week 11 (Visit 5)	Secondary	Kruskal-Wallis	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo

Endpoint	Primary/ Secondary/ Exploratory	Inference model	Comparisons of interest
CFB in MSL at Week 11 (Visit 5)	Exploratory	ANCOVA	Higher dose vs. Placebo; Lower dose vs. Placebo; Pooled active vs. Placebo

Abbreviations: ANCOVA = Analysis of Covariance; CGI-S = Clinical Global Impression of Severity; CFB = Change from Baseline; DSS = Daytime Sleepiness Scale; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MDHI = Myotonic Dystrophy Health Index; MSL = Mean Sleep Latency; PGI-S = Patient Global Impression of Severity.

11.4.2 Primary Efficacy Analysis

11.4.2.1.1 Daytime Sleepiness Scale (DSS)

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). The DSS score is the sum of the answers to questions 1 to 4 plus the reversed score to question 5 (i.e., minus the score for question 5). If at least one question is not answered, the score will be set to missing.

The DSS score can vary from 0 to 15 and the higher the score, the higher the degree of sleepiness. The questionnaire was developed and validated in patients with DM1 in three subgroups: 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 2021).

A descriptive summary of DSS (mean, SD, median, minimum, maximum) for the absolute values and change from Baseline to Week 7 and to Week 11 will be presented by treatment group and for the active groups combined. If the termination visit occurs after the Week 7 Double-Blind visit, the early termination data will be windowed to Week 11 regardless of the discontinuation reason.

The change from Baseline to Week 11 will be analyzed using a Mixed Model Repeated Measures (MMRM) approach. Fixed effects will be included for treatment, visit, treatment*visit interaction, baseline value, and stratification factor. An unstructured covariance structure will be utilized; in case of failure to converge, covariance structures TOEPH (Heterogeneous Toeplitz), ARH(1) (Heterogeneous auto-regressive 1), and VC (Variance Components) will be tested in the order specified. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

If there is more than a 10% difference between the stratification factor recorded in IRT versus the stratification factor derived from the prior and concomitant in the EDC, the MMRM analysis will be repeated using the stratification factor reported in IRT.

11.4.3 Secondary Efficacy Analyses

Descriptive summary (mean, SD, median, minimum, maximum) of each of the secondary endpoints will be provided for absolute values and for change from baseline. All summaries will be presented by treatment group and for the active groups combined.

11.4.3.1.1 Fatigue Severity Scale (FSS)

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 and Hewlett et al 2011). The 9 items are summed and then averaged (i.e., divided by 9) 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 higher the score, the more severe the fatigue is and the more it affects the person's activities.

If the number of missing items is <4, the FSS total score is derived as the mean of the non-missing items; if 4 or more items are missing, the total score is set to missing (Rosa 2014).

Early termination visits will be summarized and analyzed under Week 7 or Week 11 (depending on which visit they are closest to, see section 9.2 on visit window) regardless of the discontinuation reason.

A descriptive summary of the FSS absolute values and change from Baseline to Week 7 and to Week 11 will be reported by treatment group and for the active groups combined.

The change from Baseline will be analyzed using a Mixed Model Repeated Measures (MMRM) approach. Fixed effects will be included for treatment, visit, treatment*visit interaction, baseline value, and wake-promoting agents stratification factor. An unstructured covariance structure will be utilized; in case of failure to converge, covariance structures TOEPH (Heterogeneous Toeplitz), ARH(1) (Heterogeneous auto-regressive 1), and VC (Variance Components) will be tested in the order specified. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

11.4.3.1.2 Cogstate Detection Test

The Cogstate detection test is a computerized measure of psychomotor function and uses a validated simple reaction time (890-) 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 $\log_{10}$-transformed RTs for correct responses). Decreasing scores represent improved test performance.

Early termination visits will be summarized and analyzed under Week 11 (see section 9.2 for details on the visit window) regardless of the discontinuation reason.

A descriptive summary of Cogstate detection test for the absolute values and change from Baseline to Week 11 will be reported by treatment group and for the active groups combined.

In addition, similarly to the primary endpoint (see section 11.4.2.1.1) but without the multiple imputations, the change from Baseline will be analyzed with an ANCOVA. Fixed effects will be included for treatment, Baseline value, and stratification factor. LS means, SEs, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts. The effect size (magnitude of the differences between treatment groups and placebo) will also be provided.

The analysis of the Detection Test will be performed by Cogstate; more details are provided in the Cogstate SAP.

11.4.3.1.3 Cogstate Identification Test

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 $\log_{10}$-transformed RTs for correct responses). Decreasing scores represent improved test performance.

Early termination visits will be summarized and analyzed under Week 11 (see section 9.2 for details on the visit window) regardless of the discontinuation reason.

The same summaries and analyses as performed for Cogstate detection test will be repeated for the Cogstate identification test endpoint. Further details on the summaries and inferential analyses are provided in section 11.4.3.1.2.

The analysis of the Identification Test will be performed by Cogstate; more details are provided in the Cogstate SAP.

11.4.3.1.4 Cogstate One Back Test

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 (mean of the log_{10}-transformed RTs for correct responses). Decreasing scores represent improved test performance.

Early termination visits will be summarized and analyzed under Week 11 (see section 9.2 for details on the visit window) regardless of the discontinuation reason.

The same summaries and analyses as performed for Cogstate detection test will be repeated for the Cogstate on back test endpoint. Further details on the summaries and inferential analyses are provided in section 11.4.3.1.2.

The analysis of the One Back Test will be performed by Cogstate; more details are provided in the Cogstate SAP.

11.4.3.1.5 Myotonic Dystrophy Health Index (MDHI)

The MDHI is a disease-specific, patient-reported outcome measure for DM1. It focuses on the major symptoms experienced by patients with DM1. 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.

Each subscale score is a weighted average of its components; the prevalence of each symptom and theme (prevalence scores), and their importance to patients (impact scores) form the basis of the weights. The total score is a weighted average of the subscales where the weights are based on the population impact scores. The subscales and total scores have been validated independently (Heatwole et al 2014 and Heatwole et al 2016), and are scored on a scale of 0-100, with a higher score representing a higher burden of disease.

The questionnaires will be scored centrally (University of Rochester, Rochester, NY) and the total score and sub-scores will be provided for analysis.

Early termination visits will be summarized and analyzed under Week 7 or Week 11 (depending on which visit they are closest to, see section 9.2 on visit window) regardless of the discontinuation reason.

A descriptive summary of the MDHI total score, the fatigue sub-score, the sleep sub-score, and the cognitive impairment sub-score of the absolute values and change from Baseline to Week 7 and to Week 11 will be reported by treatment group and for the active groups combined.

The change from Baseline MDHI total score will be analyzed using a Mixed Model Repeated Measures (MMRM) approach. Fixed effects will be included for treatment, visit, treatment*visit interaction, baseline value, and wake-promoting agents stratification factor. An unstructured covariance structure will be utilized.; in case of failure to converge, covariance structures TOEPH (Heterogeneous Toeplitz), ARH(1) (Heterogeneous auto-regressive 1), and VC (Variance Components) will be tested in the order specified. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

11.4.3.1.6 Epworth Sleepiness Scale (ESS)

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).

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' (Hirshkowitz 2017). If one or more item's score is missing, the ESS score will be invalid and not be derived.

- 0-5: Lower Normal Daytime Sleepiness
- 6-10: Higher Normal Daytime Sleepiness
- 11-12: Mild Excessive Daytime Sleepiness
- 13-15: Moderate Excessive Daytime Sleepiness
- 16-24: Severe Excessive Daytime Sleepiness

A descriptive summary of ESS for the absolute values and change from Baseline to Week 7 and to Week 11 will be reported by treatment group and for the active groups combined. In addition, frequency count and percentage of the ESS score at each visit versus Baseline category will be provided by way of shift tables. Early termination visits will be summarized under Week 7 or Week 11 (depending on which visit they are closest to, see section 9.2 on visit window) regardless of the discontinuation reason.

The change from Baseline will be analyzed using a Mixed Model Repeated Measures (MMRM) approach. Fixed effects will be included for treatment, visit, treatment*visit interaction, baseline value, and wake-promoting agents stratification factor. An unstructured covariance structure will be utilized.; in case of failure to converge, covariance structures TOEPH (Heterogeneous Toeplitz), ARH(1) (Heterogeneous auto-regressive 1), and VC (Variance Components) will be tested in the order specified. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

11.4.3.1.7 Clinical Global Impression of Severity (CGI-S) of Excessive Daytime Sleepiness (EDS)

[redacted]

Numerical values in parentheses were assigned in the datasets. Early termination visits will be summarized and analyzed under Week 7 or Week 11 (depending on which visit they are closest to, see section 9.2 on visit window) regardless of the discontinuation reason.

A descriptive summary of CGI-S for the absolute values and change from Baseline to Week 7 and to Week 11 will be presented by treatment group and for the active groups combined. In addition, frequency count and percentage of the CGI-S score at each visit versus baseline category will be provided using a shift table.

The change from Baseline will be analyzed using a Mixed Model Repeated Measures (MMRM) approach. Fixed effects will be included for treatment, visit, treatment*visit interaction, baseline value, and wake-promoting agents stratification factor. An unstructured covariance structure will be utilized; in case of failure to converge, covariance structures TOEPH (Heterogeneous Toeplitz), ARH(1) (Heterogeneous auto-regressive 1), and VC (Variance Components) will be tested in the order specified. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) at each visit will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

11.4.3.1.8 Patient Global Impression of Severity (PGI-S) of Excessive Daytime Sleepiness (EDS)

[redacted]

Numerical values in parentheses were assigned in the datasets. The same summaries and analyses performed for CGI-S will be repeated for the PGI-S endpoint. Further details on the summaries and inferential analyses are provided in section 11.4.3.1.7.

11.4.3.1.9 Mean Sleep Latency

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. The MWT evaluates the magnitude of sleepiness in relationship to the underlying wakefulness system's functioning.

For the MWT, patients will be 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.

The session will end if the patient falls asleep, or if more than 40 minutes elapse without the patient falling asleep. The sleep latency, or the time it takes to fall asleep, will be recorded.

Analysis of the MWT will be based on the average MSL computed from the four sessions.

A descriptive summary of MSL for the absolute values and change from Baseline to Visit 5 will be reported by treatment group and for the active groups combined. If the termination visit occurs after the Visit4 Double-Blind visit, the early termination data will be windowed to Visit 5 regardless of the discontinuation reason.

The change from Baseline to Visit 5 will be analyzed using an ANCOVA model with fixed effect terms for treatment, baseline value, and wake-promoting agents stratification factor. Least Square means, standard errors, and the LS mean differences (each treatment versus placebo and the pooled active groups versus placebo) will be reported. All estimates will be generated from a single model, i.e., the pooled active estimates will be created via model contrasts.

11.4.3.1.10 Sustained Attention to Response Task (SART)

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 response time, are important. The total, go, and no-go scores will be summarized and analyzed. The total score is the sum of the go score and no-go score.

Early termination visits will be summarized and analyzed under Visit 5 (see section 9.2) regardless of the discontinuation reason. The actual values and change from Baseline of the go, no-go and total score will be summarized using descriptive statistics.

In addition, it is assumed that the change from Baseline in SART parameters are not normally distributed. For the difference between lower dose pitolisant and placebo, the difference between higher dose pitolisant and placebo, and the difference between pooled pitolisant and placebo, p-values will be generated and reported. Early termination visits will be summarized and analyzed under Visit 5 regardless of the discontinuation status.

11.4.4 Open-Label Extension Efficacy Analyses

The OLE efficacy parameters are:

- DSS
- ESS
- FSS
- Cogstate (Detection Test, Identification Test, One Back Test)
- MDHI Total score and sub-scores of sleep, fatigue and cognitive impairment
- CGI-S for EDS
- PGI-S for EDS

Actual and change from Baseline results in the OLE Phase will be summarized by using descriptive statistics at each open-label visit. Results will be tabulated by total. In addition, shift tables from baseline to each of the OLE visits will be provided for DSS, ESS, CGI-S and PGI-S.

11.5 PK Analyses

Concentration-time data of pitolisant and BP1.3484 will be summarized using descriptive statistics (number of observations, number of results less than the lower limit of quantification, SD, geometric mean, geometric SD, coefficient of variation [%], median, minimum, and maximum) based on the PK population in the Double-Blind Treatment Phase by randomized treatment group (lower dose and higher dose only). For summarization, plasma concentrations below the quantifiable limit (BLQ) will be set to zero.

Concentration will be listed.

11.6 Safety Analyses

Safety analyses will be provided for the Double-Blind safety and open-label safety populations. All safety data will be listed and summarized. No formal statistics will be performed for the safety analyses.

For the Double-Blind Treatment Phase, summaries will be presented by treatment arms. For the OLE Phase, results will be tabulated by treatment received during the Double-Blind Treatment Phase (including active arms pooled) and overall.

11.6.1 Adverse Events

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

A treatment-emergent AE (TEAE) is

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

For the OLE Phase, any AE starting on or after the first dose of OLE treatment will be considered treatment emergent.

A serious AE (SAE) is defined as any AE that results in any of the following outcomes: death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs 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.

An AE's relationship to study treatment will be evaluated by the Investigator. The following relationships will be collected in eCRF: definitely related, probably related, possibly related, unlikely related, or not related. AEs that are evaluated as definitely, probably, or possibly related (or with missing relationship) will be considered treatment-related AEs for summary purposes.

The severity of AEs will be classified by the Investigator as mild, moderate, or severe. If the severity is missing, the AE will be assumed to be severe.

An overall TEAE summary will be generated presenting the frequency and percentage of patients and the number of AEs for the following:

- Any TEAE
- Any treatment-related TEAE
- Any severe TEAE
- Any treatment-related severe TEAE
- Any serious TEAE
- Any treatment-related serious TAE
- Any TEAE leading to study discontinuation
- Any TEAE leading to discontinuation of investigational product (IP)
- Any TEAE leading to interruption of IP
- Any TEAE leading to death

All AEs will be coded using MedDRA; the version used will be included in the tables and listings footnotes. The TEAEs will also be summarized by system organ class (SOC) and preferred term (PT), by severity and relationship to study treatment.

The TEAE summary tables will be sorted by SOC and PT. SOCs will be displayed in descending order of overall frequency in the pooled pitolisant group and then alphabetically. PTs will be displayed in descending order of overall frequency and then alphabetically within SOC. A patient with 2 or more events within the same PT of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of patients in the safety population. The following summaries by SOC and PT will be provided:

- TEAE
- Treatment-related TEAE
- TEAE by maximum severity
- Serious TEAE
- Treatment-related serious TEAE
- TEAE leading to discontinuation of IP
- TEAE leading to interruption of IP
- TEAE leading to death

Finally, a summary of all AEs and all SAEs by SOC and PT will be provided.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment related AEs, SAEs, and AEs leading to study discontinuation.

For patients who opt to continue in the OLE Phase of the study, only AEs started on or before the last dose of the Double-Blind Treatment Phase will be included in the summaries for the Double-Blind Treatment Phase. AEs started after the last dose of treatment and up to 30 days after the last dose of treatment in the Double-Blind Treatment Phase will be included in a separate listing and summarized in the OLE Phase reporting.

For clinicaltrials.gov and other registries, the following will be produced in XML format.

1. All-Cause Mortality: *§ A table of *all* anticipated and unanticipated deaths due to any cause, with the number and frequency of such events by arm or comparison group of the clinical study.
2. Serious Treatment-Emergent Adverse Events: * A table of *all* serious adverse events, grouped by System Organ Class, with the number and frequency of such events by arm or comparison group of the clinical study.
3. Other (Not Including Serious) Treatment-Emergent Adverse Events: * A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold (for example, 5 percent) within any arm of the clinical study, grouped by organ system, with the number and frequency of such events by arm or comparison group of the clinical study.

XML schema are here: https://prsinfo.clinicaltrials.gov/RRSUploadSchema.xsd

11.6.2 Seizure Disorder

A summary of 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 presented. Patients who experience worsening of their seizure disorder will be withdrawn from the study.

A summary table of seizure will be sorted by SOC and PT. All seizure data will be presented in a data listing.

11.6.3 Clinical Laboratory Evaluations

Laboratory parameters will be summarized for Double-Blind safety population and OLE safety population. Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to the International System of Units (SI) units for reporting and processing purposes. Absolute values and changes from Baseline at each visit will be presented descriptively. Results reported as “<xx” or “>xx” will be imputed to “xx” for calculating the summary statistics.

Hematology, serum chemistry, and urinalysis will be summarized using descriptive statistics for numerical data and numbers and percentages for categorical data at each scheduled assessment. Numerical hematology, chemistry, and urinalysis results will be summarized using change from Baseline as well.

All clinical laboratory test results will be presented in data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Urine drug screen will be listed only.

11.6.4 Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, , and body temperature. Patients will be resting for at least 5 minutes before taking vital signs.

Vital signs results and corresponding change from study baseline values will be summarized at each visit using descriptive statistics by treatment group.

The reference ranges for the vitals are included in Table 8 and will be used to categorize the assessments by Normal, High, or Low. The lowest and highest post-baseline results will be compared with that at the study baseline, and the "shifts” from study baseline will be summarized using the number and percentage of patients in each shift category by treatment group.

All vital signs measurements will be presented in a data listing; height will be presented within the demographic listing.

Table 8: Vital Signs Reference Ranges

Parameter	Low	High	Normal
Systolic Blood Pressure (mmHg)	< 80	> 130	80 - 130
Diastolic Blood Pressure (mmHg)	< 60	> 90	60 - 90
Heart Rate (beat per minutes)	< 60	> 100	60 - 100
Respiration Rate (breath per minutes)	< 12	> 20	12 - 20
Temperature (°C)	< 36.6	> 37.3	36.6 -- 37.3

11.6.5 Physical Examinations

Physical examination will include an evaluation of the head and neck as well as cardiovascular, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems (SoA for DBT phase and SoA for OLE phase in the protocol Amendment 5). Abbreviated physical examinations will be performed based on patient-reported symptoms (SoA for DBT phase and SoA for OLE phase in the protocol Amendment 5).

Physical examination data will be presented in a data listing.

11.6.6 12-Lead Electrocardiograms

Triplicate 12-lead ECGs will be obtained after the patient has been resting for at least 5 minutes. For clinically significant ECG findings, a follow-up ECG should be performed within 24 hours and again 7 days later to ensure that 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.

A core ECG laboratory will manage all ECG monitoring activities. All ECG results along with the investigator's interpretation, including the average of triplicate measurements at each timepoint, will be presented in data listings.

QT values will be presented with the implementation of corrections (i.e., Fridericia's) as defined in International Council for Harmonisation (ICH) Guidelines E14 by the following categories:

Absolute QT interval corrected for heart rate based on Fridericia's formula (QTcF) interval prolongation:

- QTcF interval <450 ms
- QTcF interval 450-480 ms
- QTcF interval 480-500 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline 30-60 ms
- QTcF interval increases from baseline >60 ms

In addition, potential QT prolongations will be categorized as:

- PR interval >300 msec
- QRS duration >140 msec
- PR interval increase from baseline >50%
- QRS duration increase from baseline >40%

- HR increase >65% from baseline
- HR decrease >40% from baseline

The actual values and change from baseline values at each time point will be summarized for the safety populations. The overall interpretation will also be summarized by timepoint as well as the worst post-baseline.

The average of the triplicates at each timepoint will be used in the summaries as defined in Section 9.2.

11.6.7 Holter Monitoring

Patients will be fitted with a Holter monitor, which they will wear for 24 hours before returning the device and for all abnormal Holter monitor findings considered clinically significant by the Investigator, additional evaluation, including an unscheduled ECG, is required.

A core ECG laboratory will manage all Holter monitoring activities. All Holter results will be presented in data listings.

The actual values and change from baseline values at each time point will be summarized for the safety populations. Abnormalities will be summarized by frequency count and percentages.

11.6.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) scale is composed of 11 items answered Yes or No. The C-SSRS also includes a suicidal ideation intensity rating from 1 (least severe) to 5 (most severe).

Results of the C-SSRS will be provided in data listings only.

12 References

Doghramji K, Mitler MM, Sangal RB, et al. A normative study of the Maintenance of Wakefulness Test (MWT). Electroencephalogr Clin Neurophysiol. 1997; 103:554-62.

Heatwole C, Bode R, Johnson N, et al. Myotonic dystrophy health index: initial evaluation of a disease specific outcome measure. Muscle and Nerve. 2014; 49(6):906-14.

Heatwole C, Bode R, Johnson NE, et al. Myotonic Dystrophy Health Index: Correlations with clinical tests and patient function. Muscle and Nerve. 2016; 53(2):183-90.

Hewlett S, Dures E, Almeida C. Measures of Fatigue. Arthritis Care and Research. 2011; 63(S11):S263-86.

Hirshkowitz M and Sharafkhaneh A. Evaluating Sleepiness. in Kryger M, Roth T and Dement WC. Principles and Practice of Sleep Medicine. 6th Ed. Elsevier, Philadelphia, 2017. P 1652.

Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14(6):540-5.

Krupp LB, LaRocca NG, Muir-Nash J, et al. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989; 46:1121-23.

Laberge L, Bégin P, Montplaisir J, et al. Sleep complaints in patients with myotonic dystrophy. J Sleep Res. 2004; 13:95-100.

Laberge L and Dauvilliers Y. Myotonic dystrophy and sleepiness in Thorpy M. and Billiard M. (Eds). Sleepiness: Causes, Consequences and Treatment. Cambridge University Press; 2010: 316-26.

Laberge L, Dauvilliers Y, Bégin P, et al. Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: To lump or split? Neuromuscular Disorders 2009; 19:397-402.

Laberge L, Gallais B, Auclair J, et al. Responsiveness of Daytime Sleepiness and Fatigue Scales in Myotonic Dystrophy Type 1. Can J Neurol Sci. 2021; 20:1-4.

SAS Institute Inc. 2015. SAS 9.4 Procedures Guide. 5th ed. Cary, NC: SAS Institute Inc.

Rosa, K., Fu, M., Gilles, L. et al. Validation of the Fatigue Severity Scale in chronic hepatitis C. Health Qual Life Outcomes. 2014; 12:90. https://doi.org/10.1186/1477-7525-12-90.

13 Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ANCOVA	Analysis of covariance
ASP	Average sleep propensity
BLQ	Below the Quantifiable Limit
bpm	Beat per minutes
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTG	Cytosine-thymine-guanine
CYP	Cytochrome P450
DBT	Double-Blind Treatment
DM1	Myotonic dystrophy type 1
DSS	Daytime Sleepiness Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
H_1	Histamine 1
ICH	International Council for Harmonisation
IP	Investigational product
IRT	Interactive Response Technology
LOE	Lack of efficacy
LS	Least square
MDHI	Myotonic Dystrophy Health Index
MedDRA	Medical Dictionary for Regulatory Activities

Glossary of Abbreviations:	
mITT	Modified Intent-to-Treat
MMRM	Mixed effect model repeated measures
MSL	Mean sleep latency
MWT	Maintenance of Wakefulness Test
NIH	National Institutes of Health
OLE	Open-Label Extension
PD	Protocol deviations
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PT	Preferred term
QTcF	QT interval corrected for heart rate based on Fridericia's formula
RT	Reaction time
SAE	Serious adverse event
SAP	Statistical analysis plan
SART	Sustained Attention to Response Task
SD	Standard deviation
SE	Standard error
SI	International System of Units
SoA	Schedule of Assessment
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

14 Appendix 5 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

15 Appendix 2 Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

16 Appendix 3 Example of Prohibited Medications

Examples of strong CYP2D6 Inhibitors, strong CYP3A4 Inducers, Medications that prolongQT Interval, And Centrally Acting H1R Antagonists.

Medicaiton Type	**Example**
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_1 receptor 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

17 Appendix 4 SAS Sample Code

Below are some examples of code for inferential statistics described in the SAP.

ANCOVA:

```
 proc mixed data=datain;
      class trtpn wkprag;
      model chg = base trtpn wkprag / solution;
      lsmeans trtpn / cl stderr pdiff cov;
      estimate 'pooled vs placeco' 0.5 0.5 -1 / cl;
      ods output diffs = lsdiffs lsmeans = lsm solutionf = parms;
run;
```

MMRM:

```
 proc mixed data=datain;
     class subjid trtpn avisitn wkprag;
     model chg = base trtpn avisitn trtpn*avisitn wkprag/ ddfm=KenwardRoger;
     repeated visit / subject = subjid type = UN;
     lsmeans trtpn / cl stderr pdiff cov;
     estimate 'pooled vs placeco' 0.5 0.5 -1 / cl;
     ods output diffs = lsdiffs lsmeans = lsm solutionf = parms;
run;
```

Kruskal-Wallis Test:

```
proc npar1way data=datain wilcoxon dscf;
    class trtpn;
    var chg;
run;
```

18 Appendix 6 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 Magensium[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

Abbreviations: 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 OLE Phase.

NOTE: Wake-promoting agents including mixed amphetamine salts such as Vyvanse (lisdexamfetamine mesylate), 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.