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Approvals

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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CGI-S	Clinical Global Impression of Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire, 10 item version
H_1R	Histamine 1 Receptor
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IH	Idiopathic hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
IRT	Interactive Randomization Technology
ITT	Intent-to-Treat
LOE	Lack of efficacy
LSM	Least Square Means
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

Abbreviation	Description
MMRM	Mixed Model for Repeated Measures
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PROMIS-SRI	Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment
PT	Preferred term
SAP	Statistical analysis plan
SD	Standard deviation
SIQ	Sleep Inertia Questionnaire
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total bilirubin
TC	Telephone contact
TEAE	Treatment-emergent adverse event
TFL	Table, Figure and Listing
ULN	Upper limit of normal
WHODD	World Health Organization Drug Dictionary

2 PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure the data listings, summary tables and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1 Responsibilities

Syneos Health will perform the statistical analyses of the safety and efficacy data and is responsible for the production and quality control of all associated tables, figures, and listings. Any analyses related to exposure-response and population pharmacokinetic (PK) parameters will be described in a separate document. Analyses related to the Cogstate objectives will be described in a separate document.

2.2 Timings of Analyses

The primary analyses of safety and efficacy are planned after all patients complete the final study assessment or terminate early from the study, and after database lock.

[redacted]

Final approval of the SAP by Harmony Biosciences and by Syneos will occur prior to unblinding the Double-Blind Randomized Withdrawal Phase of the study.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of pitolisant compared with placebo in treating excessive daytime sleepiness (EDS) in patients with idiopathic hypersomnia (IH) age ≥ 18 years.

3.2 Secondary Objectives

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

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

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

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

3.3 Pharmacokinetic Objectives

The PK objective of this study is to:

- Determine the serum concentrations of pitolisant and its major inactive metabolite (BP1.3484) in patients with IH

Additional PK analyses, including population PK modeling and exposure-response analyses, may be performed and reported separately.

4 STUDY DETAILS/DESIGN

4.1 Brief Description

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

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

Following completion of the 6-week Dose Optimization Period, patients will enter the 2-week Stable Dose Period of the Open-Label Phase (weeks 7 and 8). During this period, patients will remain at their optimal dose (the same dose they were taking at the end of the Dose Optimization Period [17.8 mg or 35.6 mg]) of open-label pitolisant for 2 weeks; dose adjustments are not allowed during the Stable Dose Period. At the end of the Stable Dose Period (which is also both the end of the Open-Label Phase and the Double-Blind Randomized Withdrawal Baseline), safety, efficacy, PK, and CYP2D6 genotype assessments will be collected, [redacted] individual who has achieved a decrease of ≥3 points in their Epworth Sleepiness Scale (ESS) score from [redacted]

During the Double-Blind Randomized Withdrawal Phase, patients will receive blinded study drug at the same dose they were taking in the Stable Dose Period (17.8 mg or 35.6 mg pitolisant or matching placebo). The duration of the Double-Blind Randomized Withdrawal Phase will be 4 weeks (weeks 9-12); dose adjustments are not permitted during this phase of the study. Safety and efficacy assessments will be conducted two weeks after randomization (start of Week 11) and safety, efficacy, and blood sampling

for pitolisant and metabolite concentrations will be conducted at the end of the Double-Blind Randomized Withdrawal Phase (end of Week 12). After completion of the Double-Blind Randomized Withdrawal Phase (End-of Treatment [EOT] Visit is on Day 84, the last day of blinded treatment), patients will have the opportunity to enroll in a long-term, open-label safety study under a separate protocol. Patients who elect to not enroll in the long-term open-label safety study will complete two safety follow-up TCs with the site at 15 (±3) days and 30 (+3) days after their final dose of blinded study drug in the present study, which will include assessment for AEs and concomitant medication use.

4.2 Patient Selection

4.2.1 Inclusion Criteria

Protocol Section 4.1.1 provides a list of the inclusion criteria for the study.

4.2.2 Exclusion Criteria

Protocol Section 4.1.2 provides a list of the exclusion criteria for the study.

4.3 Determination of Sample Size

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

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

4.4 Treatment Assignment and Blinding

After completing the Open-Label Phase of the study, [redacted] 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 blinded study drug prior to being randomized in the study.

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

The study blind should not be broken except for medical emergencies when 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 premature unblinding must be clearly documented.

4.5 Administration of Study Medication

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

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

Double-Blind Randomized Withdrawal Phase: Pitolisant will be administered as a single daily dose of 17.8 mg or 35.6 mg, or matching placebo, during weeks 9 through 12.

4.6 Study Procedures and Flowchart

A flow chart depicting the overall study design and details regarding study procedures are provided in the study protocol, in Figure 1 and the Schedule of Assessments, respectively.

5 ENDPOINTS

5.1 Primary Efficacy Endpoint

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

5.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Change in the Idiopathic Hypersomnia Severity Scale (IHSS) score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Percent of patients who worsen on the Patient Global Impression of Change (PGI-C) based on symptoms of IH (PGI-C [IH]) at the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Change on the Clinical Global Impression of Severity (CGI-S) for IH from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

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- Change on the Patient-Reported Outcomes Measurement Information System, Sleep-Related Impairment v1.0 – Short Form 8a (PROMIS-SRI 8a) T-Score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.

5.3 Other Secondary Efficacy Endpoints

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

- Patient Global Impression of Severity (PGI-S) for EDS
- Functional Outcomes of Sleep Questionnaire, 10 item version (FOSQ-10)
- Sleep Inertia Questionnaire (SIQ)
- Working memory as measured by the Cogstate One Back test
- Attention as measured by the Cogstate Identification test
- Psychomotor function as measured by the Cogstate Detection test

5.4 Safety Endpoints

The safety endpoints are incidence of AEs and changes in clinical laboratory test results, vital signs, and 12-lead electrocardiogram (ECG) results.

5.5 Pharmacokinetic Endpoints

The PK endpoints are:

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

Concentrations will be summarized and listed.

6 ANALYSIS POPULATIONS

6.1 Screened Population

The Screened Population will include all patients who provide informed consent for the study. A by-patient listing of screened patients will be provided

6.2 Enrolled Population

The Enrolled Population will include all patients who meet all eligibility criteria at the start of the Open-Label Phase.

6.3 Safety Population

The Safety Population will include all patients who enter the Open-Label Phase and take at least one dose of study drug. Patients will be analyzed according to treatment received.

6.4 Intent-to-Treat Population

The ITT Population will include all randomized patients who received at least one dose of study drug after their date of randomization and who have a Double-Blind Randomized Withdrawal Baseline efficacy value (end of the Stable Dose Period). This population will be used to summarize the primary and secondary efficacy endpoints. Patients will be analyzed according to their randomized treatment assignment.

6.5 Not ITT Population

The Not ITT Population will include all patients who are part of the Safety Population but not part of the ITT Population.

6.6 Pharmacokinetic Population

The PK Population will include all patients in the Safety Population who also have at least one post-dose PK concentration of pitolisant or BP1.3484 measured.

7 ESTIMANDS

7.1 Primary Efficacy Estimand

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]

- [redacted]
  - [redacted] assumes a patient's missing data after [redacted]
  - [redacted]
- [redacted] –

- [redacted] –

7.2 Key Secondary Efficacy Estimands

The key secondary efficacy endpoints are:

- Change on the IHSS score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Percent of patients who worsen on the PGI-C based on symptoms of IH at the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Change on the CGI-S from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) for pitolisant compared with placebo.
- Change on the PROMIS-SRI 8a T-score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12)

7.2.1 IHSS Estimand

The estimand for the IHSS score key secondary efficacy endpoint is defined as:

- **Population:** Adult patients with IH
- **Analysis Population:** ITT population
- **Variable:** Change on the IHSS score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12)
- **Intercurrent Events:**
  - Discontinuation from the study – addressed using the treatment policy as follows:
    - A MMRM approach will be used, which assumes a patient's missing data after study withdrawal is MAR.
    - A tipping point sensitivity analysis may be conducted, if deemed necessary, as described in Section 10.1.2.

- All intercurrent events – addressed using the treatment-policy strategy; values will be used as observed.

- **Population-level Summary**: LSM difference in the change from the Double-Blind Randomized Withdrawal Phase Baseline in IHSS, pitolisant – placebo

7.2.2 PGI-C (IH) Estimand

The estimand for the PGI-C (IH) key secondary efficacy endpoint is defined as:

- **Population:** Adult patients with IH
- **Analysis Population:** ITT population
- **Variable:** Percent of patients who worsen on the PGI-C (IH) based on symptoms of IH at the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12)
- **Intercurrent Events:**
  - Discontinuation from the study – addressed using the treatment policy; values will be used as observed.
  - All intercurrent events – addressed using the treatment-policy strategy; values will be used as observed.
- **Population-level Summary**: Difference in proportions of patients who have worsened on the PGI-C (IH), pitolisant – placebo.

7.2.3 CGI-S (IH) Estimand

The estimand for the CGI-S for IH key secondary efficacy endpoint is defined as:

- **Population:** Adult patients with IH
- **Analysis Population:** ITT population
- **Variable:** Change on the CGI-S for IH from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12)
- **Intercurrent Events:**
  - Discontinuation from the study – addressed using the treatment policy as follows:
    - A MMRM approach will be used, which assumes a patient's missing data after study withdrawal is MAR.
    - A tipping point sensitivity analysis may be conducted, if deemed necessary, as described in Section 10.1.2.
  - All intercurrent events – addressed using the treatment-policy strategy; values will be used as observed.
- **Population-level Summary**: LSM difference in the change from the Double-Blind Randomized Withdrawal Baseline to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) in CGI-S for IH, pitolisant – placebo

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7.2.4 PROMIS-SRI 8a Estimand

The estimand for the PROMIS-SRI 8a T-Score key secondary efficacy endpoint is defined as:

- **Population:** Adult patients with IH
- **Analysis Population:** ITT population
- **Variable:** Change on the PROMIS-SRI 8a T-Score from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12)
- **Intercurrent Events:**
    - Discontinuation from the study – addressed using the treatment policy as follows:
        - A MMRM approach will be used, which assumes a patient's missing data after study withdrawal is MAR.
        - A tipping point sensitivity analysis may be conducted, if deemed necessary, as described in Section 10.1.2.
    - All intercurrent events – addressed using the treatment-policy strategy; values will be used as observed.
- **Population-level Summary**: LSM difference in the change from the Double-Blind Randomized Withdrawal Baseline to the end of the 4-week Double-Blind Randomized Withdrawal Phase (Week 12) in CGI-S for IH, pitolisant – placebo

8 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1 General Methods

Unless otherwise specified, for each endpoint, the Open-Label Phase Baseline value is the last observed measurement, whether scheduled or unscheduled, prior to open-label study drug administration. Safety and efficacy data for the Open-Label Phase will be summarized with changes (or shifts) from Open-Label Phase Baseline to each subsequent assessment week during the Open-Label Phase. Safety and efficacy data for the Double-Blind Randomized Withdrawal Phase will be summarized with changes (or shifts) from the Double-Blind Randomized Withdrawal Phase Baseline (i.e., end of the Stable Dose Period at Week 8/Visit 4) to each subsequent assessment week during the Double-Blind Randomized Withdrawal Phase.

All safety data will be presented for each phase. For the Open-Label Phase, data will be presented for ITT Population, Not ITT Population, and overall (total Safety Population). For the Double-Blind Randomized Withdrawal Phase, data will be presented by treatment group (active treatment and placebo).

Summary statistics (mean, SD, median, minimum, maximum) for the ESS score (Section 7.1) will be reported for the change from the Double-Blind Randomized Withdrawal Phase Baseline to the end of the Double-Blind Randomized Withdrawal Phase for the active treatment group and the placebo group.

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Unless otherwise specified, Open-Label Phase summary percentages will be calculated using the Safety Population as the denominator and Double-Blind Randomized Withdrawal Phase summary percentages will be calculated using the ITT Population as the denominator.

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

Relevant patient data will be included in listings. Patients will be included in patient data listings in the appropriate analysis population.

8.2 Key Definitions

8.2.1 Study Baselines

8.2.1.1 The Open-Label Phase Baseline value is defined as the last observed measurement for the specific efficacy or safety parameter, whether scheduled or unscheduled, prior to the first dose of open-label study drug administration.

8.2.1.2. The Double-Blind Randomized Withdrawal Phase Baseline is defined as the last observed measurement for the specific efficacy or safety parameter, prior to the first dose of double-blind study drug administration. This value will serve as the Double-Blind Randomized Withdrawal Phase Baseline value.

[redacted]

8.2.3 Study Day

The study day is calculated as:

Date of event – reference date + 1 if the date of the event occurs on or after the reference date or

Date of event – reference date if the date of the event occurs prior to the reference date.

The reference date for Study Day is the date of the first dose of open-label study drug (Day 1).

8.3 Missing Data

Every effort will be made to retain patients in the study; however, patients are free to withdraw from the study at any time for any reason. Patients who withdrawal early will be asked to return to the clinic for an early termination visit for completion of assessments. A MMRM analysis will be used as the main method of analysis for the primary efficacy and continuous secondary efficacy endpoints (including key secondary efficacy endpoints); an MMRM analysis assumes the data is Missing at Random (MAR). A sensitivity analysis using different missing data imputation methods may be performed at a later time, if found appropriate. See Section 10.1.2 for details.

8.4 Analysis Visit Windows

For questionnaires, laboratory test results, ECGs, and vital signs assessments, unscheduled results and results from early termination visits will be windowed for analyses based on the computed study day and will be assigned to visits that mirror the planned data collection schedule for each assessment. Analysis preference will be given to the scheduled assessments, with unscheduled and early termination assessments being used to fill in gaps where scheduled assessments are missing. Scheduled visits will be analyzed according to the nominal visit name.

The target day for each planned collection time point refers to the protocol defined collection day. In cases where multiple assessments fall into the window for a particular visit, the assessment closest to the target day will be used. In cases where multiple assessments are equally close to the target day, the earlier value will be used. If a scheduled and unscheduled or early termination assessment falls in the same window, the scheduled visit is used, regardless of distance from the target.

Appendix 1 provides details of Analysis Visit Windowing rules by assessment type.

8.5 Multiple Comparisons

8.6 Subgroups

Subgroup analyses will be performed on the primary efficacy endpoint and key secondary efficacy endpoints. Selected safety summaries will be presented by subgroups. Subgroups included will be:

- Age groups: ≥18 to <65 years vs ≥65 years
- Sex groups: Male vs Female
- Ethnicity groups: Hispanic or Latino vs Not Hispanic or Latino
- Race groups: White vs Black or African American, Asian, Other
- [redacted]

The study was not designed to detect treatment differences with high statistical power within subgroups. Note that some subgroup levels will have a small number of patients.

9 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

9.1 Analysis Populations

The number and percentage of patients in each analysis population will be summarized.

9.2 Patient Disposition and Withdrawals

The disposition data will be summarized as follows.

- Number of patients screened
- Number of patients treated in the Open-Label Phase
- Number and percentage of patients completing the Open-Label Phase as planned (defined as responder or discontinued from the study due to being a non-responder after completing Visit4/Week 8)
- Number and percentage of Open-Label completers (defined as patients who have completed all Day 56 assessments) who are responders (Responder definition is provided in Section 8.2.2)
    - Number of responders who are randomized
    - Number of responders who are not randomized, and reason
- Number and percentage of completers who are non-responders
- Number and percentage of patients prematurely discontinuing treatment during the Open-Label Phase (including reasons for premature treatment discontinuation)
- Number and percentage of patients prematurely terminating study participation during the Open-Label Phase, defined as terminated study participation prior to completing Day 56 procedures (including reasons for premature study termination)
- Number and percentage of patients treated in the Double-Blind Randomized Withdrawal Phase
- Number and percentage of patients completing the Double-Blind Randomized Withdrawal Phase (defined as completing Day 84)

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- Number and percentage of patients prematurely discontinuing treatment during the Double-Blind Randomized Withdrawal Phase (including reasons for premature treatment discontinuation)
- Number and percentage of patients prematurely terminating study participation during the Double-Blind Randomized Withdrawal Phase (including reasons for premature study termination)
- Number and percentage of patients completing the study, defined as completing the 30-day follow-up TC or completing the Double-Blind Randomized Withdrawal Phase and enrolling into the long-term open label safety study (under separate protocol HBS-101-CL-011 and SAP).

For the disposition data described above, percentages for the Open-Label Phase will be calculated using the number of patients in the Safety Population as the denominator. For the Double-Blind Randomized Withdrawal Phase, percentages will be calculated using the number of patients in the ITT Population as the denominator. Percentages for reasons for discontinuation will be calculated using the number of patients who discontinued. In addition, a figure summarizing disposition (i.e., consort diagram) will be prepared.

9.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, sex, child-bearing potential, race, ethnicity, and baseline disease characteristics will be reported for the ITT and Safety populations. Baseline disease characteristics include time since IH diagnosis and whether IH is with or without long sleep.

9.4 Medical History

A summary table of the number and percentage of patients for medical history by system organ class (SOC) and preferred term (PT) will be produced for patients in the ITT and Safety Populations. Medical history will be sorted alphabetically by SOC and PT within the same SOC using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 25.0, or later. For the summary tables, each patient is counted once under each SOC and PT category. A patient may be counted more than once if they have more than one medical history event coded under different SOC or PT categories. However, the patient will be counted only once in the overall category.

Time since IH diagnosis to informed consent date will be summarized in months. In cases where year of diagnosis is present and month is missing, July will be used for calculating number of months.

All medical history data will be listed.

9.5 Medications

Prior medications in the patient's medical record and prior and concomitant medications reported by the patient will be collected. Medications include prescription and over the counter medications (including herbal products and vitamins). For patients who elect not to enroll in the separate long-term, open-label safety study (HBS-101-CL-011), 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) will be recorded, including dose, regimen, reason for administration, and start date. For patients who elect to enroll in the long-term, open-label safety study, all medications taken by patients between signing of informed consent and first dose of study medication in the long-term, open-label safety study will be recorded, including dose, regimen, reason for administration, and start date. Medications taken after the first dose of study medication in study HBS-101-CL-011 will be summarized as part of HBS-101-CL-011. Changes in concomitant medication will be recorded in the electronic case report form (eCRF).

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Medications will be classified as prior (started prior to the first dose of study drug in the Open-Label Phase), concomitant (continued past or started on or after the first dose of study treatment in the Open-Label Phase), or both. Medications starting more than 30 days after the last dose of study drug will not be considered as concomitant.

Partial dates will be considered when determining if a medication is prior or concomitant. If the partial start or end dates are not sufficient to determine if the medication is prior, it will not be considered prior. If the partial start or end dates are not sufficient to determine if the medication is concomitant, it will be considered concomitant.

All prior and concomitant medications will be classified using the anatomical therapeutic chemical (ATC) classification coded terms and preferred drug names from the World Health Organization Drug Dictionary (WHODD), version Global B3 Mar2022 or later.

Summaries of prior and concomitant medications will be presented separately in tabular form using the level 4 ATC term as an upper classification level and the preferred drug name as a lower classification level. All medications will be summarized and sorted by most frequently reported by level 4 ATC term and preferred drug name within a given level 4 ATC term. The summary will consist of the frequency and percentage of patients in the Safety Population.

For each patient, the medication will be counted only once within a level 4 ATC term and only once under a given preferred drug name. A patient may appear more than once if they have more than one concomitant medication coded under different ATC terms or preferred drug names; however, the patient will be counted only once in the overall category.

All prior and concomitant medications will be listed.

The use of medications that may prolong the QT interval is not permitted in the study. The use of medications known to be strong CYP3A4 inducers, or centrally acting histamine 1 receptor (H_1R) antagonists is not permitted. Examples of strong CYP3A4 inducers, centrally acting H_1R antagonists, and medications that may prolong the QT interval are provided in Appendix C of the protocol. Prohibited medications taken during the study will be reported and summarized as part of the protocol deviations listing.

The presence of strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Use of strong CYP2D6 inhibitors is allowed during the study; however, if used, the maximum permitted daily dose of pitolisant is 17.8 mg. Examples of strong CYP2D6 inhibitors are provided in Appendix C of the protocol. These medications will be flagged in the medication listing after being identified by the Sponsor.

9.6 Concomitant Procedures

Nonpharmacologic therapies/procedures and changes in therapies/procedures will be recorded in the eCRF. A summary table of the number and percentage of patients for concomitant procedures by SOC and PT will be produced for patients in the ITT and Safety Populations. For patients who elect not to enroll in the separate long-term, open-label safety study (HBS-101-CL-011), all new and changed therapies/procedures recorded between signing of informed consent and the second Safety Follow-Up TC (30 +3 days after final dose of study drug) will be summarized. For patients who elect to enroll in the long-term, open-label safety study, all new and changed therapies/procedures recorded between signing of informed consent and the first dose of study medication in the long-term, open-label, safety study will be included in the summary table. Any concomitant procedures occurring after the first dose of study medication in the long-term safety study will be assessed as part of study HBS-101-CL-011. Concomitant

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medications starting more than 30 days after the last dose of study drug will not be considered as concomitant.

Concomitant procedures will be sorted alphabetically by SOC and PT within the same SOC using the MedDRA coding dictionary, version 25.0, or later version. For the summary tables, each patient is counted once under each SOC and PT category. A patient may be counted more than once if they have more than one concomitant procedure coded under different SOC or PT categories. However, the patient will be counted only once in the overall category.

All concomitant procedure data will be listed.

9.7 Extent of Exposure and Treatment Compliance

The duration of study drug exposure during the Open-Label Phase (in both days and weeks) and for the entire study will be summarized for the Safety population. The duration of study drug exposure during the Double-Blind Randomized Withdrawal Phase (in both days and weeks) will be summarized for the ITT population and for the Safety Population. Percent of patients reaching each stable dose level at the end of the Open-Label Phase will be summarized for the Safety Population.

Duration of exposure = date of last dose in study/phase – date of first dose in study/phase + 1

Descriptive statistics will be provided for duration of exposure (n, mean, SD, median, minimum, and maximum).

Duration of exposure data will be listed.

9.8 Treatment Compliance

Treatment compliance (in both days and weeks) during the Open-Label Phase and for the entire study will be summarized for the Safety Population. Treatment compliance during the Double-Blind Randomized Withdrawal Phase (in both days and weeks) will be summarized for the ITT Population. Number and percent of patients will be presented for treatment compliance categories of <80%, ≥80 to ≤120%, and >120%.

Treatment compliance% = 100*(Total number of doses taken) / (Total number of doses expected)

Doses taken = the number of tablets taken during in study/phase (i.e., sum of the tablets taken as reported on the eCRF)

Doses expected = (assigned dose level / bottle dose level) times the number of days from first dose to last efficacy assessment [date of last efficacy assessment in study/phase – date of first dose in study/phase + 1]

E.g., when assigned dose level is 8.9 mg and bottle dose level is 4.45 mg, patients are expected to take 2 tablets per day. When assigned dose level is 17.8 mg and bottle dose level is 17.8 mg, patients are expected to take 1 tablet per day.

Treatment compliance data will be listed.

9.9 Protocol Deviations

A guidance document for identifying major deviations was developed during the conduct of the study. Protocol deviations were reviewed monthly by Clinical Operations and Clinical Development and the

guidance document was updated as additional major deviations were identified. The guidance document was finalized prior to database lock.

Prior to database lock, major deviations were reviewed by the Sponsor and categorized as Important if they may have impacted the study conclusions.

Protocol deviations during the Open-Label Phase that are classified as "Major" will be summarized for the Safety Population. Protocol deviations during the Double-Blind Randomized Withdrawal Phase that are classified as "Major" will be summarized for the ITT population. All protocol deviations will be listed.

10 EFFICACY

10.1 Primary Efficacy Endpoint

Summary statistics (mean, SD, median, minimum, maximum) for the ESS score (Section 7.1) will be reported for the change from the Double-Blind Randomized Withdrawal Phase Baseline (Week 8) to the end of the Double-Blind Randomized Withdrawal Phase for the active treatment group and the placebo group.

A Mixed Model for Repeated Measures model will yield unbiased results under the assumption that data are missing at random. The change from Double-Blind Randomized Withdrawal Phase Baseline (i.e., end of the Stable Dose Period) will be analyzed in an MMRM analysis. Fixed effects will be included for treatment, Double-Blind Randomized Withdrawal Phase Baseline value, visit and a term for the interaction between treatment and visit. An unstructured covariance structure will be utilized; Kenward-Rogers degrees of freedom will be used. Least square means (LSMs), standard errors, and the LSM differences will be reported.

10.1.1 Sample Size Re-estimation Analysis

[redacted]

[redacted]

10.1.2 Sensitivity Analysis

[redacted]

[redacted]

10.2 Key Secondary Efficacy Endpoints

Analyses of the key, alpha-controlled, continuous secondary efficacy endpoints (IHSS, Section 7.2.1, CGI-S [IH], Section 7.2.3, and PROMIS-SRI 8a, Section 7.2.4) will utilize an approach identical to the one provided for the primary efficacy analysis, including any imputation methodology. A tipping point sensitivity analysis, if performed, where patients who discontinue from the study due to an AE or LOE will be analyzed using all possible scores for the assessment will also be conducted on these key secondary efficacy endpoints as described in Section 10.1.2.

An MMRM will be used for continuous key secondary efficacy endpoints (e.g., for IHSS). A tipping point sensitivity analysis will be conducted at a later time, if found appropriate.

Subscale scores for IHSS will be calculated as follows and will be presented in a listing:

- Subscale 1: Daytime Functioning = sum of items 5, 9, 10, 11, 12, 13, 14
- Subscale 2: Long Sleep Duration and Sleep Inertia = sum of items 1, 2, 3, 4, 8
- Subscale 3: Napping = sum of items 6 and 7

For analyses of PGI-C [IH] (Section 7.2.2), the number and percentage of of patients in the "Worsened" category for each treatment group will be reported. A patient is considered as "Improved/No Change" if they record a response of "A Little Better", "Much Better", or "No Change". Patients with responses of "A Little Worse" or "Much Worse" are considered "Worsened". The groups will be compared with a difference in proportions z-test using the categories described above.

For this binary key secondary efficacy endpoint, a tipping point sensitivity analysis may be conducted at a later time. The tipping point sensitivity analysis (using the same type of difference in proportions z-test) would be done by conducting an analysis for each of the possible sets of hypothetical outcomes (for patients with missing data at a given visit, such as the Day 84, Week 12 analysis visit) of patient counts of "Worsened" and "Improved/No Change" for each of the two Double-Blind randomized treatment groups.

Groups will be compared using the difference in proportions z-test. Subgroups with sufficiently small 2x2 table expected cell counts will be compared using Fisher's Exact test.

10.3 Other Secondary Efficacy Endpoints

10.3.1 Patient Global Impression of Severity for EDS

Responses to the PGI-S (for EDS) will be mapped as 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, and 5 = Very Severe.

Summary statistics (n, mean, SD, median, minimum, maximum) for the observed values and for the change from the Double-Blind Randomized Withdrawal Phase Baseline to the end of the Double-Blind Randomized Withdrawal Phase will be reported for the PGI-S for the active treatment group and the placebo group.

10.3.2 Functional Outcomes of Sleep Questionnaire, 10 item version

Summary statistics (n, mean, SD, median, minimum, maximum) for the observed values and for the change from the Double-Blind Randomized Withdrawal Phase Baseline to the end of the Double-Blind

Randomized Withdrawal Phase will be reported for the FOSQ-10 total score for the active treatment group and the placebo group.

Total and subscale scores will be calculated as follows, using non-zero responses only:

- Subscale 1: Activity level = mean of items 6, 8, 9
- Subscale 2: Vigilance = mean of items 3, 4, 7
- Subscale 3: Intimacy and Sexual Relationships = item 10
- Subscale 4: General Productivity = mean of items 1, 2
- Subscale 5: Social Outcomes = item 5
- Total = 5 * mean of Subscales 1 through 5

Responses to individual items will be listed.

10.3.3 Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment

Raw scores will be converted to a T-Score for the primary analysis using the conversion table from the PROMIS Sleep-Related Impairment Scoring Manual. Summary statistics (n, mean, SD, median, minimum, maximum) for the raw values and the T-Scores and for the change from the Double-Blind Randomized Withdrawal Phase Baseline to the end of the Double-Blind Randomized Withdrawal Phase will be reported for the PROMIS-SRI 8a T-Score for the active treatment group and the placebo group. The version of PROMIS-SRI 8a used in this study is PROMIS® Item Bank v1.0 – Sleep-Related Impairment – Short Form 8a.

Responses to individual items will be listed. Total scores will be listed in both raw value and T-Score.

10.3.4 Sleep Inertia Questionnaire

For the SIQ, in addition to calculating the total score, the following subscales scores will be calculated:

- Physiological (sum over items 4, 5, 7, 8, 9, 10, 11, 12)
- Responses to Sleep Inertia (sum over items 1, 2, 3, 6, 15)
- Cognitive (sum over Items 16, 17, 18, 19, 21)
- Emotional (sum over items 13, 14, 20)

Summary statistics (n, mean, SD, median, minimum, maximum) for the observed values and for the change from the Double-Blind Randomized Withdrawal Baseline to the end of the Double-Blind Randomized Withdrawal Phase will be reported for the SIQ total score, each subscale score, the time (minutes) it takes to 'come to' in the morning (Item 22), and how many days per week this happens (Item 22b) for the active treatment group and the placebo group.

Responses to individual items will be listed.

10.3.5 Analysis of Other Secondary Efficacy Endpoints

In addition to the summaries listed above, the other secondary efficacy endpoints (PGI-S for EDS, FOSQ-10 total score, adjusted PROMIS-SRI 8a total score, and SIQ total score) will also be analyzed in an MMRM model, similar to the primary efficacy endpoint.

10.3.6 Cogstate Tests

Analyses related to the Cogstate objectives will be described in a separate document.

10.4 Supportive Efficacy Assessments

Patient assessment of overall change in their EDS will be measured using the PGI-C (EDS). Patient interviews will be conducted during Visit 5 after completion of the safety and efficacy assessments and/or procedures. Analyses of these supportive assessments will be described in a separate document.

11 PHARMACOKINETICS

PK concentrations at all collected time points will be included in the patient listings. Serum concentrations of pitolisant and BP1.3484 during specific intervals after dosing (0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-20, 20-24, >24 h after the last dose) will be summarized.

CYP2D6 metabolizer status will be summarized.

12 SAFETY

The Safety Population will be used for the safety analyses. Safety is assessed by monitoring the incidence of AEs and changes in clinical laboratory test results, vital signs, C-SSRS assessment, 12-lead ECG results, and physical examination findings from signing of informed consent through 30 days after final dose of study drug. For responders who continue into the separate long-term, open-label, safety study (HBS-101-CL-011), safety will be assessed up to the first dose of study medication in the long-term safety study, after which safety will be assessed as part of study HBS-101-CL-011.

All safety data will be presented for each phase. For the Open-Label Phase, data will be summarized for ITT Population, Not ITT Population, and overall. For the Double-Blind Randomized Withdrawal Phase, data will be summarized by treatment group and overall.

C-SSRS and physical examination findings will be listed, not summarized.

12.1 Adverse Events

Adverse events that start during or up to 30 days after the last dose of study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered treatment-emergent adverse events (TEAEs). For patients who elect to enroll in the separate long-term safety study (HBS-101-CL-011), AEs that start or worsen up to 30 days after the last dose of study drug administered during study HBS-101-CL-010, but after the date of the first dose of study drug in the long-term safety study, will be summarized as part of the long-term safety study. All TEAEs will be coded and tabulated by SOC and PT. MedDRA version will be specified in the table footers.

TEAEs in non-responders and TEAEs in responders with start date/worsening prior to the first dose of study drug in the Double-Blind Randomized Withdrawal Phase will be associated with the Open-Label Phase. TEAEs in responders with start date/worsening on or after the first dose of study drug in the Double-Blind Randomized Withdrawal Phase will be associated with the Double-Blind Randomized Withdrawal Phase.

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In the event of a partial start date for an adverse event, the following imputation rules will be used solely to determine whether the AE is a TEAE and the phase in which it is associated. In listings, only actual dates will be included.

- Only the day is missing (month and day are present)
  - Month and year are the same as the month and year of the first dose of study drug
    - Impute missing start date as the date of the first dose of study drug; AE will be considered treatment emergent and will be associated with the Open-Label Phase.
  - Month and year are not the same as the month and year of the first dose of study drug
    - Day will be imputed to the first of the month.
- The month is missing, but the year is present
  - Year is the same as the year of the first dose of study drug
    - Impute missing start date as the date of the first dose of study drug; AE will be considered treatment emergent and will be associated with the Open-Label Phase.
  - Year is not the same as the year of the first dose of study drug
    - Impute missing month as January and missing day as the 1st of the month.
- The year is missing
  - Impute any missing elements to the corresponding element in the date of the first dose of study drug. If entire date is missing, impute missing start date as the date of the first dose of study drug; AE will be considered treatment emergent and will be associated with the Open-Label Phase.

- In any of the above cases, if the imputed start date is imputed as a date that is after the end date, then the imputed date will be changed to coincide with the end date of the AE.

Adverse events will be summarized with number of patients and percentages. For summaries by SOC and PT, a patient will be counted only once for each SOC and for each PT. Summaries by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

For summaries by SOC, PT, and maximum severity, a patient is counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level. Adverse events with missing severity will be considered severe when determining highest severity level and for presentation in summary tables.

An AE is summarized as treatment-related if it is classified as definitely related, probably related, or possibly related in the eCRF by the Investigator. Adverse events with missing relationship to study drug will be considered treatment-related for summary tables.

The following summaries of TEAEs will be produced for each study phase:

- An overall summary of the number and percentage of patients reporting TEAEs, serious TEAEs, treatment-related TEAEs, treatment-related serious TEAEs, TEAEs leading to discontinuation of

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study treatment, treatment-related TEAEs leading to discontinuation of study treatment, and TEAEs leading to death
- TEAEs overall and by SOC and PT
- Treatment-related TEAEs overall and by SOC and PT
- TEAEs by maximum intensity, overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- TEAEs leading to discontinuation of study treatment, overall and by SOC and PT
- Treatment-related TEAEs leading to study drug discontinuation by PT
- Treatment-related serious TEAEs by PT

All AEs will be listed. Serious adverse events, adverse events leading to discontinuation of treatment, adverse events leading to study withdrawal, and deaths will be listed separately. AEs will be flagged in the listings to identify treatment-emergent or not treatment-emergent.

An Extensible Markup Language (XML) file of all AEs and all nonserious AEs will be produced.

12.2 Laboratory Evaluations

Laboratory summaries will be presented for each study phase.

Observed values and change from Baselines (as defined in Section 8.2.1) will be summarized by scheduled visit for serum chemistry, hematology, and continuous urinalysis parameters included in Table 1. All other parameters will be presented in listings. Shift tables from Open-Label Baseline clinical grade (low, normal, high) will be produced for chemistry and hematology. Standard reference ranges are defined by the laboratory and will be included in the listings.

For all laboratory tests, individual patient values will be listed and values outside of the laboratory-defined standard reference range will be flagged.

A listing of patients meeting laboratory-based Hy's law criteria will be provided. To aid in the identification of potential Hy's Law cases, the following 3 lab parameter criteria will be programmed and presented in the listings.

1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3 x the upper limit of normal (ULN)
2) Total bilirubin (TBL) elevation of >2 x ULN
3) Alkaline phosphatase (ALP) <2 x ULN or is missing

Table 1: Clinical Laboratory Tests

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

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

12.3 Vital Signs

Vital sign summaries will be presented for each study phase.

Observed values and change from Open-Label Phase Baselines (as defined in Section 8.2.1) to scheduled visits will be summarized by scheduled visit for vital signs parameters.

Vital sign values will be listed, and abnormal values will be flagged.

12.4 Electrocardiogram

Electrocardiogram summaries will be presented for each study phase.

Observed values and change from Open-Label Phase Baseline or change from Double-Blind Randomized Withdrawal Phase Baseline based on local ECG results will be summarized by scheduled visit for ECG parameters (heart rate and PR, RR, QRS, and QT).

Two sets of QTcF values and 2 QTcB values are provided in listings:

-Site-provided QTcF/QTcB: Values that were entered in eCRF by the site, which were either calculated by the ECG machine or by the site.

-Derived QTcF/QTcB: Values that were programmatically derived (using the standard formulas for QTcF and QTcB) based on RR and QT values entered in eCRF by the site.

Derived QTcF and QTcB values will be summarized in the tables. The listings will include both derived and site-provided QTcF and QTcB values.

Categorical summaries based on QTcF will be provided to show changes from Open-Label Phase Baseline in QTcF 30-60 msec, >60 msec, and actual values >450 msec for male patients and >470 msec for female patients, as well as QTcF >500 msec regardless of gender at each scheduled visit.

For all ECG parameters, individual patient values will be listed and the above QTcF categories will be flagged.

12.5 Physical Examination

Physical examination results will be listed.

12.6 Columbia-Suicide Severity Rating Scale

Results of the C-SSRS will be listed.

13 INTERIM ANALYSIS

[redacted]

[redacted]



[redacted]

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- [redacted]
- [redacted]
- [redacted]

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[redacted]

14 CHANGES FROM ANALYSES PLANNED IN PROTOCOL

The protocol states that the primary analysis will be conducted with a Multiple Imputation approach. Lack of convergence issues for the multiple imputation analyses led to the use of a Mixed Model for Repeated Measures (MMRM) approach instead as the main method to be applied for the continuous primary and secondary efficacy endpoints (including key secondary efficacy endpoints).

[redacted]

PROMIS-SRI 8a endpoint (using T-scores) has been added as a key secondary endpoint.

The IHSS subscales are redefined to align with new scientific material that has been updated since earlier versions of the HBS-101-CL-010 protocol and this SAP (Rassu et al., 2022). The description of the IHSS in the protocol is superseded by the following: The IHSS is a self-administered questionnaire with a total of 14 items that assess long sleep duration and sleep inertia (5 items), daytime functioning (7 items), and napping (2 items).

15 REFERENCE LIST

Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999; 55(3):853-7.

Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomized trial. Lancet Neurol. 2013; 12(11):1068-75.

FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. FDA-2001-D-0219 (March 2006).

Lawrence J, Hung HMJ. Estimation and confidence intervals after adjusting the maximum information. Biometrical Journal. 2003; 45(2):143-52.

Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999 ; 55 :1286-90.

Mehta CR and Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med. 2011; 30:3267-84.

Rassu LA, Evangelista E, Barateau L, et al., Idiopathic Hypersomnia Severity Scale to better quantify symptoms severity and their consequences in idiopathic hypersomnia. Journal of Clinical Sleep Medicine. 2022;18(2):617-629.

16 PROGRAMMING CONSIDERATIONS

16.1 General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs, or each output will be stored in a separate file.
- Output files will be delivered in Word format and/or portable document format (pdf).
- Numbering of TFLs will follow the ICH E3 guidance.

16.2 Table, Figure, and Listing Format

16.2.1 General

- All TFLs will be produced in landscape format on American letter size unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Tables and Listings will be in black and white (no color), unless otherwise specified. Figures will use distinct colors for treatment and result groupings.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2 Headers

- All output will have the following header at the top left of each page:
- Harmony Biosciences, LLC Protocol HBS-101-CL-010 (Syneos Health study number 7033836)

- Draft/Final Run <date>
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table).
- The date the output was generated will appear along with the program name as a footer on each page.

16.2.3 Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

16.2.4 Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, 'unit' will be included in the column or row heading, when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be placebo first for placebo-controlled studies and active comparators first for active comparator trials, followed by a total column (if applicable).

16.2.5 Body of the Data Display

16.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;

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- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

16.2.5.2 Table Conventions

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented; therefore, counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxxx', where xxxx is the value rounded to 4 decimal places. If the p-value is less than 0.0001, then it is presented as <0.0001. If the p-value is returned as >0.9999, then it is presented as >0.9999.
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). If a value rounds down to 0.0, then it will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.

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- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values that cannot be estimated will be reported as '-'

- The percentage of patients will normally be calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, which is usually the relevant number of patients exposed. Details will be described in footnotes or programming notes, as necessary.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.

- Where a category with a subheading (such as SOC) needs to be split over more than one page, the subheading will be followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.

- Missing data will be represented on patient listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate.

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient will be output as 'N/A', unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

16.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis.

16.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc., if a reference footnote. Each new footnote will start on a new line, where possible.
- Patient-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly (i.e., only when they add value to the readability and/or interpretability of the TFL). If more than six lines of footnotes are planned, then a cover page may be used to display footnotes; in such a case, only those footnotes that are essential to aid comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed.
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

17 QUALITY CONTROL

[redacted]

[redacted]

18 APPENDIX 1: ANALYSIS VISIT WINDOWS

ECGs:

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 84	Randomization +22 to End of Study	84	Randomization Day + 22	End of Study

Labs (all except Pregnancy Test):

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 84	Randomization +22 to End of Study	84	Randomization Day + 22	End of Study

Labs, Pregnancy Test:

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 22	Day 1 to 39	22	1	39
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 84	Randomization to End of Treatment	84	Randomization Day + 1	End of Study

Vital Signs:

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 22	Day 1 to 39	22	1	39
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 84	Randomization + 22 to End of Treatment	84	Randomization Day + 22	End of Study

This document is confidential.

Questionnaires:

ESS and C-SSRS

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 8	Day 8 to 11	8	8	11
Day 15	Day 12 to 18	15	12	18
Day 22	Day 19 to 25	22	19	25
Day 29	Day 26 to 32	29	26	32
Day 36	Day 33 to 39	36	33	39
Day 43	Day 40 to 46	43	40	46
Day 50	Day 47 to 52	50	47	52
Day 56	Day 53 to Randomization	56	53	Randomization Day
Day 71	Randomization + 8 to Randomization + 21	71	Randomization Day + 8	Randomization Day + 21
Day 84	Randomization + 22 to End of Study	84	Randomization Day +22	End of Study

IHSS, FOSQ-10, PROMIS-SRI 8a, SIQ, PGI-S

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 71	Randomization + 8 to Randomization + 21	71	Randomization Day + 8	Randomization Day + 21
Day 84	Randomization + 22 to End of Study	84	Randomization Day + 22	End of Study

CGI-S (for IH)

VISIT	RANGE	TARGET DAY	LOW	HIGH
Screening	Day -28 to -2	-28		
Visit 2	Day -1	-1		-1
Day 22	Day 8 to 39	22	8	39
Day 56	Day 40 to Randomization	56	40	Randomization Day
Day 71	Randomization + 8 to Randomization + 21	71	Randomization Day + 8	Randomization Day + 21
Day 84	Randomization + 22 to End of Study	84	Randomization Day + 22	End of Study

PGI-C (for IH)

VISIT	RANGE	TARGET DAY	LOW	HIGH
Day 71	Randomization + 8 to Randomization + 21	71	Randomization Day + 8	Randomization + 21

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Day 84	Randomization + 22 to End of Study	84	Randomization Day + 22	End of Study

PGI-C (EDS)

VISIT	RANGE	TARGET DAY	LOW	HIGH
Day 56	Day 40 to Randomization	56	40	Randomization Day

19 APPENDIX 2: EXAMPLE SAS CODE FOR ANALYSES

Harmony HBS-101-CL-010 SAP Text_v3.0_clean_20230928

Final Audit Report 2023-09-28

Created:	2023-09-28
By:	[redacted]
Status:	Signed
Transaction ID:	[redacted]

"Harmony HBS-101-CL-010 SAP Text_v3.0_clean_20230928" History

Document created by [redacted]
2023-09-28 - 4:14:36 PM GMT- IP address: [redacted]

Signer [redacted] entered name at signing as [redacted]
2023-09-28 - 4:18:05 PM GMT- IP address: [redacted]

[redacted] authenticated with Adobe Acrobat Sign.
2023-09-28 - 4:18:06 PM GMT

Document e-signed by [redacted]
Signing reason: I am the author
Signature Date: 2023-09-28 - 4:18:07 PM GMT - Time Source: server- IP address: [redacted]

Document emailed to [redacted] for signature
2023-09-28 - 4:18:08 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.
2023-09-28 - 4:25:36 PM GMT

Signer [redacted] entered name at signing as [redacted]
2023-09-28 - 4:25:39 PM GMT- IP address: [redacted]

Document e-signed by [redacted]
Signing reason: I am the reviewer
Signature Date: 2023-09-28 - 4:25:41 PM GMT - Time Source: server- IP address: [redacted]

Document emailed to [redacted] for signature
2023-09-28 - 4:25:43 PM GMT

Email viewed by [redacted]

2023-09-28 - 10:30:12 PM GMT- IP address: [redacted]

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2023-09-28 - 10:30:37 PM GMT

Document e-signed by [redacted]

Signing reason: I am the approver

Signature Date: 2023-09-28 - 10:32:12 PM GMT - Time Source: server- IP address: [redacted]

Agreement completed.

2023-09-28 - 10:32:12 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony by clicking on 'Click to Sign' button.

2023-09-28 - 10:32:12 PM GMT

DocuSign Envelope ID: [redacted]

Statistical Analysis Plan - Cogstate

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

Protocol Number: HBS-101-CL-010

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

Address: Cogstate, Inc.
Level 4, 195 Church Street
New Haven, CT, USA, 06510

SAP Version: v1.0
SAP Date: 28 Sept 2023
Protocol Version: HBS-101-CL-010, Amendment 4, Version 5.0

DocuSign Envelope ID: [redacted]

1. Note

Cogstate has prepared a Statistical Analysis Plan (SAP) for the Sponsor to review and approve for study HBS-101-CL-010. Analyses will be provided after this document has been finalized and officially signed. Text in italics is taken directly from the protocol. For more details, refer to the study protocol.

2. Version History

Version Number	Date	Reason for Revision
1.0	28 Sept 2023	Initial Version

3. Signature Page for SAP Approval

The following signatures indicate the approval of the statistical analysis plan for the data Cogstate is responsible for analysing in study HBS-101-CL-010.

Cogstate

Name (print): [redacted]

Position: [redacted]

Signature: _____

Date (DD-MMM-YYYY): _____

[redacted]

Harmony Biosciences

Name (print): [redacted]

Position: [redacted]

Signature: _____

Date (DD-MMM-YYYY): _____

[redacted]

DocuSign Envelope ID: [redacted]

Cogstate

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DocuSign Envelope ID: [redacted]

5. Abbreviations

Abbreviation	Description
ADSL	ADaM Subject-Level Analysis Dataset
ADQRS	ADaM Questionnaire, Rating, and Scale Analysis Dataset
ANCOVA	Analysis of Covariance
CI	Confidence Interval
DBRW	Double-Blind Randomized Withdrawal
DET	Detection Test
DM	Demographics
ESS	Epworth Sleepiness Scale
FT	Functional Test CDISC Domain
IDN	Identification Test
IH	Idiopathic Hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
LS	Least Square
mITT	Modified Intent-to-Treat
ONB	One Back Test
QS	Questionnaire CDISC Domain
RCI	Reliable Change Index
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SV	Subject Visits
TLF	Tables, Listings, and Figures
WSD	Within-Subject Deviation

6. Introduction

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analyses described in the study HBS-101-CL-010 protocol related to the Cogstate computerized battery and includes detailed procedures for executing the statistical analyses of the Cogstate battery data.

The SAP will be finalized and signed prior to database lock.

Any changes from the analyses planned in the Cogstate SAP will be justified in the Cogstate statistical report.

7. Study Endpoints Related to Cogstate

The Cogstate related objective is to assess the impact of pitolisant in patients with IH on cognitive function. Working memory, attention, and psychomotor function as measured by Cogstate tests are secondary efficacy endpoints for this study.

8. Study Design

8.1. General Description

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

After completion of the Screening Period, eligible patients will be enrolled in the Open-Label Phase of the study. The Open-Label Phase of the study will be 8 weeks, which includes a 6-week Dose Optimization Period and a 2-week Stable Dose Period. In the Dose Optimization Period, all patients will be titrated to their optimal dose of open-label pitolisant (17.8 mg or 35.6 mg) based on Investigator assessment of tolerability and efficacy.

[redacted]

During the Double-Blind Randomized Withdrawal Phase, patients (approximately 64 patients per treatment group) will receive blinded study drug at the same dose they were taking in the Stable Dose Period (17.8 mg or 35.6 mg pitolisant or matching placebo). The duration of the Double-Blind Randomized Withdrawal Phase will be 4 weeks (weeks 9-12). Safety and efficacy assessments will be conducted two weeks after randomization (start of Week 11) and safety, efficacy, and PK assessments will be conducted at the end of the Double-Blind Randomized Withdrawal Phase (end of Week 12). After completion of the Double-Blind Randomized Withdrawal Phase (End-of-Treatment [EOT] Visit is on Day 84, the last day of blinded treatment), patients will complete two safety follow-up TCs with the site at 15 (±3) days and 30 (+3) days after their final dose of blinded study drug, which will include assessment for AEs and concomitant medication use; patients will also have the opportunity to enroll in a long-term, open-label safety study under a separate protocol.

Figure 1 of the protocol includes a depiction of the study's schematic design.

8.2. Scheduled Visits

Table 1: Visit Schedule for Cogstate Computerized Cognitive Battery

Study Phase	Study Day/Visit	Target Day	Visit Window Lower Limit	Visit Window Upper Limit	Analysis Visit
Open-Label Phase	Visit 2 (Day -1) Familiarization 1				No, unless mapped to baseline if Visit 2 (Day -1) Baseline and Visit 2 (Day -1) Familiarization 2 are missing
	Visit 2 (Day -1) Familiarization 2				No, unless mapped to baseline if Visit 2 (Day -1) Baseline is missing
Open-Label Phase	Visit 2 (Day -1) Baseline	-1		-1	Yes
Double-Blind Randomized Withdrawal Phase	Visit 4 (Day 56)	56	40	Randomization Day	Yes; data for scheduled visit (i.e., not unscheduled or ET) should always be used if available. If data are available for more than one scheduled Visit 4 (Day 56), then rules described in Section 9.5 should be followed.
Double-Blind Randomized Withdrawal Phase	Visit 5 (Day 84) EOT	84	Randomization Day +22	End of Study	Yes; data for scheduled visit (i.e., not unscheduled or ET) should always be used if available. If data are available for more than one scheduled Visit 5 (Day 84) EOT, then rules described in Section 9.5 should be followed.
-	ET				Only if remapped to study visit if data for scheduled visit is missing or as a result of rules described in Section 9.5

-	Unscheduled Visit 1				Only if remapped to study visit if data for scheduled visit is missing or as a result of rules described in Section 9.5
-	Unscheduled Visit 2				Only if remapped to study visit if data for scheduled visit is missing or as a result of rules described in Section 9.5
-	Unscheduled Visit 3				Only if remapped to study visit if data for scheduled visit is missing or as a result of rules described in Section 9.5

9. Analysis Set and Population

9.1. Unblinding Procedure

Section 4.3 of study HBS-101-CL-010 protocol describes the unblinding procedure as it pertains to the Double-Blind Randomized Withdrawal (DBRW) Phase. Once all data discrepancies within the Cogstate eSource Platform are resolved with the clinical research units, the study database has been locked, and the study has been unblinded, then Cogstate will receive randomization codes from the sponsor or designee. Blinding is not applicable in the Open-Label Phase of the study.

9.2. Analysis Sets

9.2.1. Safety Population

The Safety Population will include all patients who enter the Open-Label Phase and take at least one dose of study drug.

9.2.2. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all randomized patients who received at least one dose of study drug after the date of randomization and who have a Double-Blind Randomized Withdrawal Baseline efficacy value (end of the Stable Dose Period). This population will be used to summarize the primary and secondary efficacy endpoints. Patients will be analyzed according to their randomized treatment assignment.

9.2.3. Not ITT Population

The Not ITT Population will include all patients who are part of the Safety Population but not part of the ITT Population.

9.3. Sample Size

The sample size in the Double-Blind Randomized Withdrawal Phase of the study is approximately 128 ITT patients randomized in a 1:1 ratio to one of two treatment groups (optimal dose of pitolisant [17.8 mg or 35.6 mg] or placebo). These estimates are based on the feasibility of enrollment and the goal of achieving statistically significant results for the effect of pitolisant on the symptom of EDS in patients with IH. The sample size is powered to show statistical significance with respect to the primary efficacy endpoint. Further details are described in the Statistical Analysis Plan for Interventional Studies: Protocol Number HBS-101-CL-010, version 3.0.

9.4. Handling of Missing Data

No imputations will be performed in the event of missing data due to dropouts or omitted visits for Cogstate endpoints.

All incomplete patient profiles will be retained in the dataset. In view of issues of reliability, all analyses will be conducted on tests that have passed completion.

9.5. Handling of Duplicate Data

Data tagged for a scheduled visit (i.e., not unscheduled or ET) should always be used if available. In cases where multiple assessments exist for the same scheduled visit, the assessment closest to the target day will be used. In cases where multiple assessments are equally close to the target day, the earlier value will be used.

When no data tagged for a given scheduled visit are available, then data from unscheduled or ET should be used if they fall into the analysis visit window for a particular visit. In cases where multiple assessments exist within the same analysis visit window, the assessment closest to the target day will be used. In cases where multiple assessments are equally close to the target day, the earlier value will be used.

9.6. Multiple Comparisons

Multiple comparisons will not be addressed since the Cogstate computerized cognitive test battery does not involve the primary or key secondary efficacy endpoints. All p-values reported for this endpoint are considered nominal.

10. Baseline Definition and Outcome Measures

10.1. Open-Label Phase Baseline

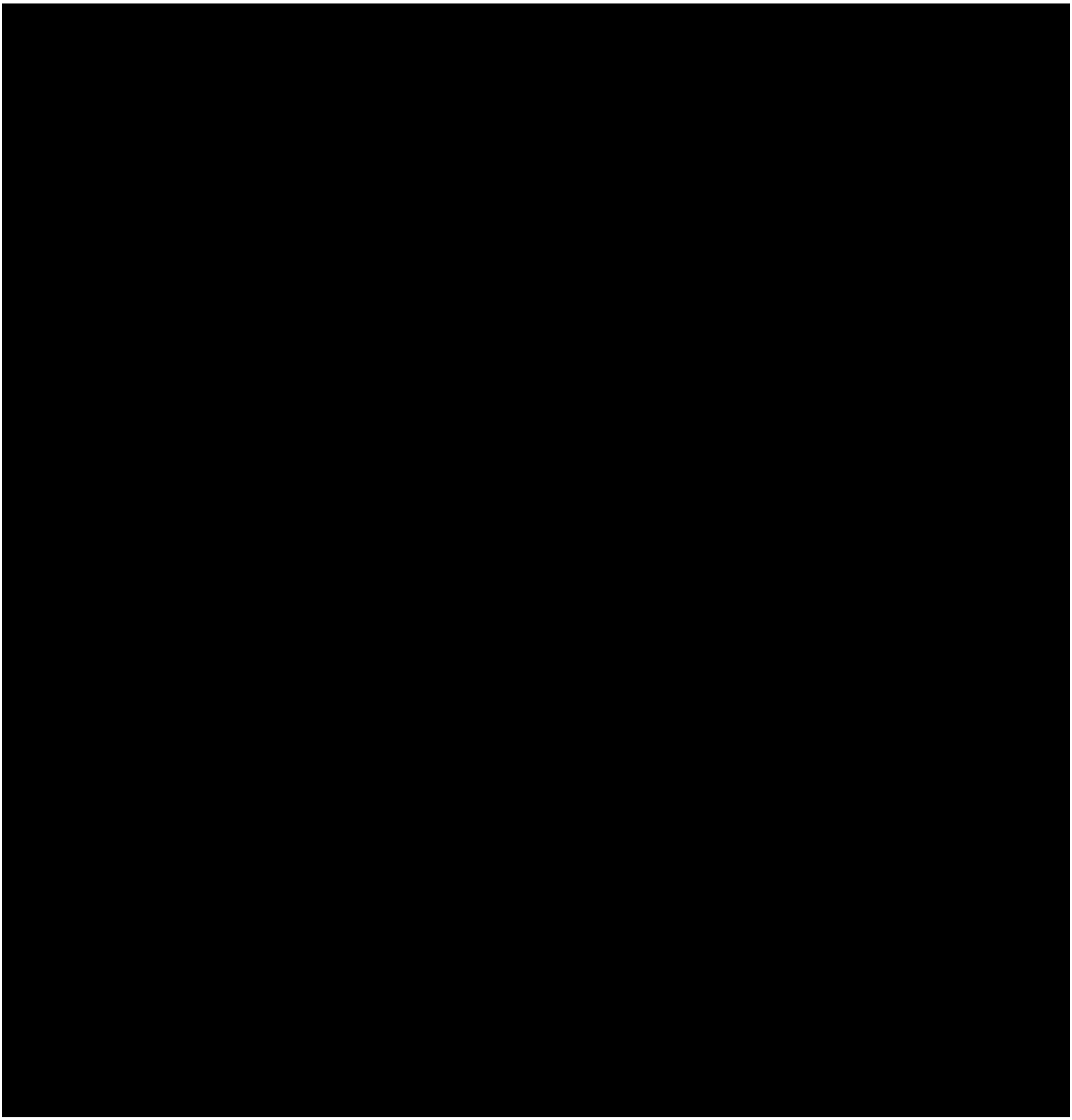
The Open-Label Phase Baseline value is defined as the last observed measurement for the specific efficacy or safety parameter, whether scheduled or unscheduled, prior to the first dose of open-label study drug administration.

This corresponds to the following in Cogstate analyses: Data associated with Visit 2 (Day -1, Baseline) will serve as Open-Label Phase Baseline. If Visit 2 (Day -1) is missing, then Visit 2 (Day -1) Familiarization 2 will serve as Open-Label Phase Baseline. If Visit 2 (Day -1) Familiarization 2 is missing, then Visit 2 (Day -1) Familiarization 1 will serve as Open-Label Phase Baseline.

10.2. Double-Blind Randomized Withdrawal Phase Baseline

The Double-Blind Randomized Withdrawal Phase Baseline is defined as the last observed measurement for the specific efficacy or safety parameter (among patients who are considered responders), prior to the first dose of double-blind study drug administration.

This corresponds to the following in the Cogstate analyses: Data associated with Visit 4 (Day 56) will serve as Double-Blind Randomized Withdrawal Phase Baseline. However, nothing prior to this visit will be used for Baseline.



[redacted]

10.4. Other Outcome Measures

10.4.1. Domain Scores

[redacted]

[redacted]

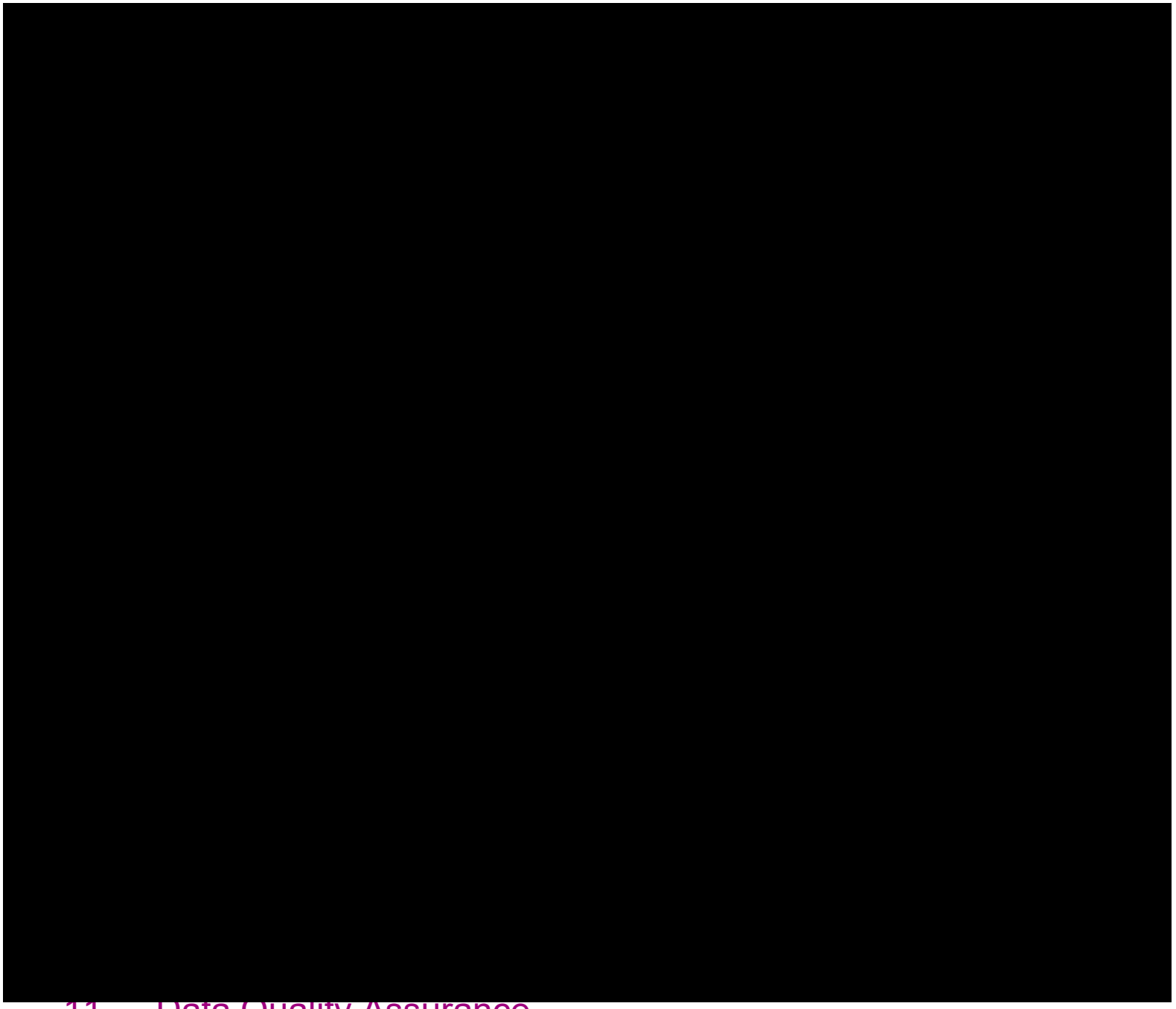
10.5. Derived Variables

10.5.1. Effect Size

[redacted]

10.5.2. Standardized Scores: Comparison of Individual Scores to Double-Blind Randomized Withdrawal Phase Baseline Data

[redacted]



11. Data Quality Assurance

Cogstate Computerized Tests

Data from the Cogstate Battery will be collected on computers at site(s) and uploaded to the Cogstate database for processing. Cogstate data management staff will query any data discrepancies. Queries will be confirmed and resolved with the sponsor, as needed.

11.1. Test Completion Criteria

For each of the Cogstate tests, subjects must provide sufficient responses to allow computation of reliable performance measures. For the majority of Cogstate tests, the term “sufficient” has been defined as a Test Completion criterion.

The number of trials required for Test Completion is unique to each test. They do not vary for different patient groups or study samples.

The completion criteria set forth a priori for each test were:

- ONB: The subject provided 100% of the correct responses required (31) for the test to terminate
- IDN: The subject provided 100% of the correct responses required (30) for the test to terminate
- DET: The subject provided 100% of the correct responses required (35) for the test to terminate

12. Analysis Overview

Cogstate is responsible for reporting final analysis results from the Cogstate Battery to explore the effect of pitolisant on cognitive function.

12.1. Analyses

12.1.1. Sample Performance at Open-Label Phase Baseline Relative to Normative Data

To characterize the overall cognitive profile of the sample prior to treatment, a table including sample mean standardized scores computed relative to Cogstate age-matched normative data will be generated for each test at the Open-Label Phase Baseline.

This normative sample for subjects aged 18 to 99 years (clustered into 18-34, 35-49, 50-59, 60-69, 70-79, 80-89 and 90-99 year age bins) is based on a healthy population of Cogstate subjects enrolled in a series of clinical trials, research, and academic studies. Irrespective of where the data originate, only baseline sessions are included in the normative database and only a single session is included for each subject. Given the evidence for limited gender differences on the Cogstate battery, the normative data are collapsed across gender within each age bin (Cromer et. al., 2015). Data are also collapsed across global geographic regions given the evidence to suggest sound cross-cultural equivalence of performance on Cogstate tests (Hammers et. al., 2012, Yoshida et. al., 2011).

12.1.2. Open-Label Phase

Cognitive outcome measures (from the Cogstate Battery), scores, and change from Open-Label Phase Baseline scores to End of Open-Label Phase scores (directionality adjusted to ensure positive scores reflect improvement), will be tabulated descriptively (n, mean, median, SD, min, max, Q1 and Q3) by test.

All change scores from the Open-Label Phase Baseline to the End of Open-Label Phase will be plotted with boxplots for each test.

[redacted]

A patient listing including scores and change from baseline scores on each test and domain score will be generated.

12.1.3. Double-Blind Randomized Withdrawal Phase

Cognitive outcome measures (from the Cogstate Battery and domain score), scores, and change scores from the Double-Blind Randomized Withdrawal Baseline to the End of the Double-Blind Randomized Withdrawal Phase (directionality adjusted to ensure positive scores reflect improvement), will be tabulated descriptively (n, mean, median, SD, min, max, Q1 and Q3) by treatment for each test and domain score.

All change scores from the Double-Blind Randomized Withdrawal Baseline to End of the Double-Blind Randomized Withdrawal Phase will be plotted with boxplots by treatment group for each test and domain score.

Change from the Double-Blind Randomized Withdrawal Baseline to the End of the Double-Blind Randomized Phase will also be analyzed using an Analysis of Covariance (ANCOVA). Fixed effects will be included for treatment and Double-Blind Randomized Withdrawal Baseline value. Least square means (LSMs), standard errors, and the LSM differences will be reported, along with 95% confidence intervals. Effect sizes, computed using the modeled LSMs, will be tabulated for each cognitive outcome measure.

A patient listing including scores and change from baseline scores on each test and domain score will be generated.

All analyses will be done in SAS (v9.4). Appendix 2 provides an example of the tables, listing, and figures (TLF) (Section 15).

13. References

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum.

Crawford, J. R., & Howell, D. C. (1998). Regression equations in clinical neuropsychology: An evaluation of statistical methods for comparing predicted and obtained scores. *Journal of Clinical and Experimental Neuropsychology*, *20*, 755–762.

Cromer, J., Schembri, A., Harel, B., & Maruff, P. (2015). The nature and rate of cognitive maturation from late childhood to adulthood. *Frontiers In Psychology, 6.*

Falleti, M. G., Maruff, P., Collie, A., & Darby, D. G. (2006). Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1095-1112.

Hammers, D. B., Jung, M., P., Pressler, S. J., Sullivan, B., Koelling, T., & Giordani, B. (2012). Clinical utility of auditory memory testing in a heart failure population. *Journal of Cardiovascular Nursing, 28*, 444-452.

Hinton-Bayre, A. D. (2010). Deriving reliable change statistics from test–retest normative data: Comparison of models and mathematical expressions. *Archives of Clinical Neuropsychology*, *25*(3), 244-256.

Yoshida, T., Suga, M., Arima, K., Muranaka, Y., Tanaka, T.,…Hashimoto, K. (2011). Criterion and Construct Validity of the CogState Schizophrenia Battery in Japanese Patients with Schizophrenia. *PLos ONE, 6,* 1-7.

14. Appendix 1: Sample SAS Code

[redacted]

15. Appendix 2: Tables, Listings, and Figures (TLF) Mock Shells

Note: the TLF numbers below may be subject to change.

TLF Number	Title
Table 14.2.9	Summary of Cogstate Population Analyzed
Table 14.2.10	Summary of Z-scores by Test at Open-Label Baseline
Table 14.2.11	Frequencies of Reliable Change Index Scores ≤ -1.65 on 2 or More Tests and Reliable Change Index Scores ≥ 1.65 on 2 or More Tests at the End of Open-Label Phase
Table 14.2.12	Cogstate One Back Test (log 10 msec) - Summary and Change from Open-Label Baseline to End of Open-Label Phase
Figure 14.2.12	Cogstate One Back Test (log 10 msec) – Boxplot of Change from Open-Label Baseline to the End of Open-Label Phase
Table 14.2.13	Cogstate One Back Test (arcsine sqrt % correct) - Summary and Change from Open-Label Baseline to End of Open-Label Phase
Figure 14.2.13	Cogstate One Back Test (arcsine sqrt % correct) – Boxplot of Change from Open-Label Baseline to the End of Open-Label Phase
Table 14.2.14	Cogstate Identification Test (log 10 msec) - Summary and Change from Open-Label Baseline to End of Open-Label Phase
Figure 14.2.14	Cogstate Identification Test (log 10 msec) – Boxplot of Change from Open-Label Baseline to the End of Open-Label Phase
Table 14.2.15	Cogstate Detection Test (log 10 msec) - Summary and Change from Open-Label Baseline to End of Open-Label Phase
Figure 14.2.15	Cogstate Detection Test (log 10 msec) – Boxplot of Change from Open-Label Baseline to the End of Open-Label Phase
Table 14.2.16	Cogstate One Back Test (log 10 msec) - Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Figure 14.2.16	Cogstate One Back Test (log 10 msec) – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Table 14.2.17	Cogstate One Back Test (arcsine sqrt % correct) - Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Figure 14.2.17	Cogstate One Back Test (arcsine sqrt % correct) – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Table 14.2.18	Cogstate Identification Test (log 10 msec) - Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase

TLF Number	Title
Figure 14.2.18	Cogstate Identification Test (log 10 msec) – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Table 14.2.19	Cogstate Detection Test (log 10 msec) - Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Figure 14.2.19	Cogstate Detection Test (log 10 msec) – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Table 14.2.20	Cogstate Psychomotor/Attention Domain Score – Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Figure 14.2.20	Cogstate Psychomotor/Attention Domain Score – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Table 14.2.21	Psychomotor/Attention/Working Memory Domain Score – Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Figure 14.2.21	Psychomotor/Attention/Working Memory Domain Score – Boxplot of Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase
Listing 16.2.6.4.1	Listing of Cogstate Data for all Subjects across all Timepoints

Table 14.1
Summary of Cogstate Population Analyzed

Study Phase	Treatment	N
Open-Label	ITT Population	xxx
	Not ITT Population	xxx
	Overall	xxx
Double Blind Randomized Withdrawal	Pitolisant	xxx
	Placebo	xxx

Table 14.2
Summary of Z-scores by Test at Open-Label Baseline
(Safety Population)

	ONB (speed)			ONB (accuracy)			IDN			DET		
Timepoint	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
OL Baseline	xxx	x.xx	x.xx	xxx	x.xx	x.xx	xxx	x.xx	x.xx	xxx	x.xx	x.xx

OL = Open-Label
Higher score represents better performance relative to normative data.

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Table 14.4.1.1
Cogstate One Back Test (log 10 msec) - Summary and Change from Open-Label Baseline to End of Open-Label Phase
Open-Label Phase
(Safety Population)

	ITT Population (N=XXX)	Not ITT Population (N=XXX)	Overall (N=XXX)
OL Baseline[a,b]			
n	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
End of OL Phase (Week 8, Day 56)[b]			
n	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Change from OL Baseline to End of 8-week OL Phase (Day 56)[c]			
n	xx	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

SD = standard deviation; OL = Open-Label
a OL Baseline is defined as Visit 2 (Day -1). If Visit 2 (Day -1) is missing, then Visit 2 (Day -1) Familiarization 2 will serve as OL Baseline. If visit 2 (Day -1) Familiarization 2 is missing, then Visit 2 (Day -1) Familiarization 1 will serve as OL Baseline.
b Lower score is better performance.
c Greater change from baseline score represents improved performance.

Source: Listing xx.x.xx, Dataset: *[NAME]*, Program: xxxxxx.sas, Output: xxxx.rtf, Generated on: YYYY-MM-DDTHH:MM
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Additional notes:

Footnote b will change depending on the test. ONB (accuracy): Higher score is better performance. ONB (speed), IDN, and DET: Lower score is better performance.

Same table shell will be used for the ONB (accuracy), IDN, and DET tests.

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Table 14.4.5.1

Cogstate One Back Test (log 10 msec) - Summary and Change from Double-Blind Randomized Withdrawal Phase Baseline to End of Double-Blind Randomized Withdrawal Phase

Double-Blind Randomized Withdrawal Phase

(Intent-to-Treat Population)

	Pitolisant (N=XXX)	Placebo (N=XXX)
DBRW Baseline[a,b]		
n	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
End of DBRW Phase (Week 12)[b]		
n	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x
Change from DBRW Baseline to end of 4-week DBRW Phase[c]		
n	xx	xx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x
Q1, Q3		xx.x, xx.x
Min, Max		xx.x, xx.x
LS Mean (SE)[d]	xx.xx (xx.xxx)	xx.xx (xx.xxx)
95% Confidence Interval[d]	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
p-value[e]	0.xxxx	0.xxxx
Difference in Change from DBRW Baseline to end of 4-week DBRW Phase[f]		
LS Mean Difference (SE)[g]	xx.xx (xx.xxx)	
95% Confidence Interval[g]	(xx.xxx, xx.xxx)	
p-value[g,e]	0.xxxx	
Effect Size[h]	x.xx	

LS = Least squares; SE = Standard error; SD = Standard deviation; DBRW = Double-Blind Randomized Withdrawal
[a] DBRW Baseline is defined as Visit 4 (Day 56).
[b] Lower score is better performance.
[c] Greater change from baseline score represents improved performance.
[d] LS means, standard errors, confidence intervals, and p-values are from an ANCOVA on the response variable change from baseline. Fixed effects were included for treatment and Double-Blind Randomized Withdrawal Phase Baseline value.
[e] * .01 to .05, ** .001 to <.01, *** <.001
[f] Positive score is better performance on pitolisant.
[g] p-values, LS mean differences and associated confidence intervals are presented for treatment arm minus placebo arm.
[h] Effect size is derived from Cohen's d. Cohen's d equals the LS mean difference between active treatment groups and placebo, and then dividing the result by the pooled standard deviation.
Effect size |d|: <0.2 considered as trivial, 0.2-0.5 considered as small, >0.5-0.8 considered as moderate, >0.8-1.1 considered as large, >1.1 considered as very large.

Source: Listing xx.x.xx, Dataset: [NAME], Program: xxxxxx.sas, Output: xxxx.rtf, Generated on: YYYY-MM-DDTHH:MM
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Additional Notes:

Footnote b will change depending on the test. ONB (accuracy): Higher score is better performance. ONB (speed), IDN, and DET: Lower score is better performance.

The same table shell will be used for the IDN and ONB tests, as well as for the Psychomotor/Attention Domain Score and the Psychomotor/Attention/Working Memory Domain Score.

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Listing 16.1
Listing of Patients for All Treatments across all Timepoints

Treatment	Patient	Study Phase		Timepoint[d]	Assessment Date/Time	Cogstate One Back Test (ONB speed)	Cogstate One Back Test (ONB accuracy)	Cogstate Identification Test (IDN)	Cogstate Detection Test (DET)	Psychomotor /Attention Domain Score	Psychomotor /Attention/ Working Memory Domain Score
Pitolisant	xxxxxxxxx	Screening	Score	Visit 2 (Day -1) Familiarization 2#	DD/MM/YYYY ##:##	x.xx	x.xx	x.xx	x.xx		
		Open-Label	Score [a]	Visit 2 (Day -1)	DD/MM/YYYY ##:##	x.xx	x.xx	x.xx	x.xx		
				Visit 4 (Day 56)##	DD/MM/YYYY ##:##	x.xx	x.xx	x.xx	x.xx		
			Change from Baseline [b]	Visit 4 (Day 56)		x.xx	x.xx	x.xx	x.xx		
			RCI Score	Visit 4 (Day 56)		x.xx*	x.xx+	x.xx	x.xx+		
		Double-Blind Randomized Withdrawal	Score [a]	Visit 5 (Day 84) EOT	DD/MM/YYYY ##:##	*	*	x.xx	x.xx	x.xx	x.xx
			Change from Baseline [b]	Visit 5 (Day 84) EOT				x.xx	x.xx	x.xx	x.xx
Placebo	xxxxxxxxx	Open-Label	Score [a]	Visit 2 (Day -1)#	DD/MM/YYYY ##:##	x.xx	x.xx	x.xx	x.xx		
				Visit 4 (Day 56)##	DD/MM/YYYY ##:##	x.xx	x.xx	x.xx	x.xx		
			Change from Baseline [b]	Visit 4 (Day 56)		x.xx	x.xx	x.xx	x.xx		
			RCI Score	Visit 4 (Day 56)		x.xx	x.xx	x.xx*	x.xx*		
		Double-Blind Randomized Withdrawal	Score [a]	Visit 5 (Day 84) EOT	DD/MM/YYYY ##:##	x.xx	x.xx	*	x.xx	x.xx	x.xx
			Change from Baseline [b]	Visit 5 (Day 84) EOT		x.xx	x.xx		x.xx	x.xx	x.xx
...	...	...	...	...	...	...	...	...	...	...	...

Asterisk (*) in a blank cell = record excluded from analysis due to assessment completion failure

[a] For ONB (speed), IDN, DET, and Domain Scores: Lower score is better performance. For ONB (accuracy): Higher score is better performance.

[b] Greater change from baseline represents improved performance.

[redacted]

[d] A single # above timepoint name denotes baseline used for Open-Label Phase, ## denotes baseline used for Double-Blind Randomized Withdrawal Phase.

Note: Where possible all data will be reported in a single line without wrapping to an additional line(s).