

Jazz Pharmaceuticals, Inc.
Statistical Analysis Plan - Protocol JZP258-407

STATISTICAL ANALYSIS PLAN

VERSION: 2.0
DATE: 09 SEP 2024

STUDY DRUG:
JZP258 (XYWAV; calcium, magnesium, potassium, and sodium oxybates)

PROTOCOL/STUDY NUMBER:
JZP258-407-03 (21 MAY 2024)

STUDY TITLE:
A Prospective, Open-Label, Single-Arm, Multicenter Study to Evaluate the Effect of Low-Sodium Oxybate Oral Solution (XYWAV) on Sleepiness, Polysomnography, and Functional Outcomes in Adult Participants Aged 18 to 75 Years with Idiopathic Hypersomnia or Narcolepsy

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses to be conducted for Protocol *JZP258-407* titled “A Prospective, Open-Label, Single-Arm, Multicenter Study to Evaluate the Effect of Low-Sodium Oxybate Oral Solution (XYWAV) on Sleepiness, Polysomnography, and Functional Outcomes in Adult Participants Aged 18 to 75 Years with Idiopathic Hypersomnia or Narcolepsy” for inclusion in the Clinical Study Report (CSR). The current version is based on Protocol *JZP258-407-03* dated 21 MAY 2024. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final CSR.

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution was developed as a low-sodium formulation of XYREM® (sodium oxybate) oral solution and contains the same active moiety, oxybate (GHB), at the same concentration as XYREM. XYWAV was approved for the treatment of Idiopathic Hypersomnia (IH) and treatment of narcolepsy based on different placebo-controlled, randomized phase 3 clinical trials.

To evaluate the efficacy of XYWAV more comprehensively, a prospective, multicenter, single-arm, open-label interventional study is designed here. A sample size of 60 male and female participants aged 18 to 75 with IH or narcolepsy (Type 1 or Type 2) will be recruited to complete the study. Participants may be taking oxybate (XYWAV, XYREM, or other oxybate medication) at study entry, be oxybate naïve, or have previously taken oxybate with or without additional antiepileptics and/or alerting agents. The study duration will be approximately 10 to 21 weeks [REDACTED] from signing the ICF to the end of the Safety Follow-up Period, including a period of 5-12 weeks [REDACTED] of treatment of XYWAV.

The impact of treatment with XYWAV on participants’ sleepiness, PSG measurements, daytime and nighttime symptoms, PK (in narcolepsy), and PROs will be evaluated in the study, many of which have not been previously studied. This will be the first evaluation of the effects of XYWAV on sleep architecture in patients with IH or narcolepsy.

This study will provide a better understanding of the impact of sleep quality on patient health, cognition, mood, and health-related quality of life after treatment with XYWAV and will be informative for health care providers choosing between treatment options for patients with IH or narcolepsy.

2. STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate excessive daytime sleepiness, measured using the Epworth Sleepiness Scale (ESS), in participants with IH or narcolepsy treated with XYWAV. Secondary and exploratory objectives for each cohort, and related endpoints and assessments, are described in Section 3 of the Protocol.

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3. STUDY DESIGN

3.1. Summary of Study Design

This is a prospective, multicenter, single-arm, open-label interventional study of participants with IH or narcolepsy (Type 1 or Type 2). Details of study design and study population are provided in Section 4 and 5 of the Protocol.

3.2. Study Treatment

Enrolled participants are assigned to treatment with XYWAV, the only study intervention in this study. Details of study intervention and treatment are provided in the Section 6 of the study protocol.

3.3. Power and Sample Size Considerations

The target sample sizes of at least 30 completers in each of the IH and narcolepsy cohorts and up to 40 completers [REDACTED] were not determined using statistical criteria.

Adjusting for anticipated discontinuation rates (20% for narcolepsy and 40% for IH), applying a 25% screen failure rate for the narcolepsy cohort and a 30% screen failure rate for the IH cohort, and accounting for participants in the narcolepsy cohort [REDACTED] approximately 72 participants with IH and 72 participants with narcolepsy will be enrolled (ie, sign the ICF). Adjusting for anticipated discontinuation rates during the Titration Period for the [REDACTED] (20%), and applying a 25% screen failure rate, up to 63 participants will be enrolled into the [REDACTED].

Epworth Sleepiness Scale

In Phase 3 randomized-withdrawal studies of XYWAV treatment in narcolepsy (Bogan, 2021) and IH (Dauvilliers, 2022), the estimated effect sizes from the treatment-withdrawal arms were 0.641 and 1.43, respectively. At the target sample size ($n = 30$) in each cohort, these effect sizes correspond to 92.4% and >99% power for statistical significance, respectively.

Stage Shifts to Wake and N1

Analyses of a recent Phase 3 study investigating fixed-dose sodium oxybate in oxybate-naïve participants (Roth, 2022) suggest potential effect sizes of 0.525 (stimulant users) and 1.01 (non-users) at the 7.5 g/night dose, and 0.928 (stimulant users) and 1.03 (non-users) at the 9.0 g/night dose. At the target sample size ($n = 30$) in each cohort, these effect sizes represent 79% to >99% power for statistical significance.

Duration of N3 Sleep

Analyses of a recent Phase 3 study investigating fixed-dose sodium oxybate in oxybate-naïve participants (Roth, 2022) suggest potential effect sizes of 0.834 at the 7.5 g/night dose and 0.933 at the 9.0 g/night dose. At the target sample size ($n = 30$) in each cohort, these effect sizes correspond to >99% power for statistical significance.

Nocturnal Awakenings

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Analyses from Phase 3 studies investigating sodium oxybate ([Roth 2017](#); [Black, 2009](#)) suggest potential effect sizes of 0.52-0.55 at the 9.0 g/night dose. At the target sample size ($n = 30$) in each cohort, this effect size corresponds to 77.9%-84.2% power for statistical significance.

Idiopathic Hypersomnia Severity Scale

In a Phase 3 randomized-withdrawal study of XYWAV treatment in IH ([Dauvilliers, 2022](#)), the estimated effect size from the treatment-withdrawal arm was 1.43. At the target sample size ($n = 30$) in each cohort, this effect size corresponds to >99% power for statistical significance.

3.4. Randomization and Blinding

This is an open-label, single-arm study without randomization or data blinding.

3.5. Interim Analysis

For publication purposes and for periodic study monitoring, ad hoc analyses of accumulating data (i.e., disposition, baseline characteristics, description of primary and secondary endpoints, and safety data) may be conducted.

4. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Analysis Set	Description
Enrolled Set	All participants who sign the ICF. This analysis set will be used to summarize participant enrollment, disposition, and protocol deviations.
Washout Set	All participants who enroll in the study and undergo a washout period for current oxybate use during the Screening Period. This analysis set will be used to summarize the safety and tolerability endpoints.
Safety Set	All participants who enroll in the study and take at least one dose of XYWAV after the Baseline Period. This analysis set will be used to summarize the safety and tolerability endpoints.
Completer Set	All participants who enroll in the study, take at least one dose of XYWAV after the Baseline Period, complete the Stable Dose Period, and complete the V4 PSG EoT Visit. This analysis set will be used for primary analyses of effectiveness endpoints.
Effectiveness Set	All participants who enroll in the study, take at least one dose of

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Analysis Set	Description
	XYWAV after the Baseline Period, and complete any EoT Visit (V4 PSG or ED). This analysis set will be used for supplemental analyses of effectiveness endpoints.
PK Analysis Set	All participants with narcolepsy who complete a PK Visit. The PK analysis set will be used to analyze the PK data, including within-visit safety endpoints.

5. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines (ICH 1998).

5.1. General Methods

Assessments of all study endpoints will be summarized descriptively. Categorical variables (e.g., race, ethnicity) will be reported as frequency and percent. Continuous variables will be reported as number of participants, mean, SD, median, minimum, and maximum (eg, age, weight). All summaries, statistical analyses, and individual participant data listings will be performed with SAS version 9.4 or later (SAS Institute, Inc.; Cary, NC). Tables, Listings, and Figures (TLFs) specifications are in another document which is incorporated by reference.

5.2. Definitions

5.2.1. Baseline

For all safety assessments and efficacy summaries across the study, baseline will be defined as the last non-missing measurement collected/assessed (scheduled or unscheduled) during Baseline Period before the first dose of XYWAV in the Titration Period.

5.2.2. Study Day

For Narcolepsy and IH cohorts, Study Day 1 will be the date of the first dose of XYWAV in the Flexible Titration Period. [REDACTED]

[REDACTED] Because the study intervention is provided and expected to be taken at night on the same day as the post-PSG morning assessments at baseline for visit V2, study day will be calculated as follows:

- If the assessment or event date is before the first dose date of study intervention in the Flexible Titration Period:
 - Study Day = Assessment/event date minus date of first study intervention
- If the assessment or event date is on the first dose date of study intervention in the Flexible Titration Period:

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- Study Day = -1
- If the assessment or event date is after the first dose date of study intervention in the Flexible Titration Period
 - Study Day = Assessment/event date minus date of first study intervention, plus 1

Similarly, assessments performed after midnight during overnight PSG or PK visits, study visits, periods, and epochs should be generally be programmed to align with the PSG/PK visit.

5.2.3. Visit Windows

Visits and visit windows are specified in the Protocol Section 1.3 (Schedules of Activities).

Unless otherwise specified, all data will be summarized using the CRF visit at which the data was collected. If a participant early discontinues, ED Visit should be conducted as soon as possible after last study dose of XYWAV (or preferably while still be on treatment), data should be mapped to the next scheduled visit at which those data would have been captured, based on the Schedule of Assessments.

Unscheduled visits in general will not be mapped (excluded from analyses) when the corresponding scheduled visit is present. Unscheduled visits will only be mapped when the scheduled visit is missing. If more than 1 unscheduled assessments are available, choose the one with the assessment date closer to the target study day specified below, if 2 assessments are equally close to the target day (but on different sides), the latter assessment will be chosen.

If multiple assessments or measurements are recorded within a single visit window (including unscheduled, repeated, and retest assessments or measurements), the following rules will be applied to determine which assessment or measurement will be used for the summaries for that analysis visit.

- If there are two or more results within the same visit window, then the latter one will be used in the analysis.
- If two or more observations are equidistant from the scheduled period day, then the observation with the latest collection date will be used in the analysis.
- If two or more observations are collected on the same day and this day is the closest to the scheduled period day, then the observation with the earliest collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

5.2.4. Nocturnal PSG Sleep Period

Nocturnal PSG sleep period, based on PSG parameters, is defined using the full night TST parameter from the PSG summary database.

5.2.5. Missing and Partial Data

Participants who drop out will not be replaced. All reported data will be included in the summaries without imputation of any missing data. Analysis datasets will include derived

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records for last observed value to facilitate supplemental analyses in which participants who discontinue the study are included.

Missing or partially missing start and stop dates for adverse events and concomitant medications will be imputed where necessary according to rules defined in [Appendix 1](#) and [Appendix 2](#). Listings will include verbatim dates as entered.

In Demographics summary tables, the age entered by the sites will be used. If it is missing, then it will be derived from date of birth and informed consent date if available. For countries where regulations allow only the year of birth to be entered for birth date, July 1st of that year will be used for the calculation of age.

Where indicated, imputation rules for multi-item summary scores are specified below.

5.3. Hypothesis Testing

Formal hypothesis testing will be conducted using the Completer Set for the following four endpoints in the Narcolepsy cohort:

- Total ESS Score (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta < 0$
- Number of stage shifts from N1/N2/N3/REM to Wake and N2/N3/REM to N1 (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta < 0$
- Duration of N3 sleep (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta > 0$
- Total number of awakenings (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta < 0$

Formal hypothesis testing will be conducted using the Completer Set for the following two endpoints in the Idiopathic Hypersomnia cohort:

- Total ESS Score (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta < 0$
- Total IHSS Score (Change from Baseline)
 - $H_0: \Delta = 0$; $H_A: \Delta < 0$

5.4. Level of Significance & Multiplicity Adjustment

Multiplicity control will be achieved using a sequential testing strategy. Listed endpoints will be tested in the order given above. Hypothesis tests with one-sided $p < 0.025$ in the expected direction will be considered statistically significant. If any ordered endpoint should fail to reject the null hypothesis, subsequent hypothesis tests will be considered nominal. Hypothesis tests for endpoints not included in the sequential testing procedure will be considered nominal.

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5.5. Subgroups and Subgroup Analyses

Summary output tables will report results separately by cohort (Narcolepsy, IH [REDACTED]). Subgroup reporting may be performed for primary, secondary, and safety endpoints for the following:

- All Cohorts:
 - Oxybate use at enrollment (sodium oxybate, generic sodium oxybate, fixed-dose sodium oxybate, low-sodium oxybate, oxybate naïve)
 - Dose of XYWAV during Stable Dose Period
- Narcolepsy Cohort:
 - Narcolepsy subtype (Type 1 vs. Type 2)
- IH Cohort:
 - Baseline PSG nocturnal sleep time (long sleep time [>9 hr] vs. without long sleep time [≤ 9 hr])¹

[REDACTED]

[REDACTED]

[REDACTED]

Additional subgroups may be added to the SAP prior to database lock.

5.6. Changes to Planned Analyses

N/A

6. STUDY POPULATION SUMMARIES

Study population summaries will be created separately for Narcolepsy, IH [REDACTED] cohorts.

6.1. Enrollment

The total number and percentage of participants for each Analysis Set will be summarized. The number of participants who enrolled by country and study site/investigator will be summarized.

6.2. Participant Disposition

Disposition of all participants who provide informed consent will be accounted in this study. For each period, the number and percentages of participants who entered, completed, are still ongoing (for interim analyses), or discontinued will be presented using the Enrolled Set. Reasons

¹ American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed.). <https://doi.org/10.1176/appi.books.9780890425596>

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for screen failure and early discontinuation will be presented in descending order of frequency; participants with missing reasons will be reported as the last row.

6.3. Demographic and Baseline Characteristics

Demographic and other baseline characteristics data will be summarized using descriptive statistics for the Safety Set, Completer Set, and PK Set.

6.4. Medical/Surgical History

Medical history will be obtained by the investigator or a medically qualified designee (consistent with local regulations). All active conditions and any condition diagnosed within the participant's lifetime that the investigator deems clinically significant should be recorded.

Medical history will be programmatically imputed using Medical History entries and any "ongoing" AE entries from the original cohort.

Surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 27.0 or later, and summarized by system organ class (SOC) and preferred term (PT) using the Safety Set.

If a participant reports a medical condition/disease, surgery, or medication more than once within a SOC or PT, the entry will be reported only once for that SOC or PT.

6.5. Prior and Concomitant Medications

The investigator or medically qualified designee should review the participant's prior medication use. All medication currently taken by the participant should be recorded.

The Prior and Concomitant Medications CRF page is available at the screening visit for these participants, but study sites may not re-enter all prior and concomitant medications. Prior and Concomitant Medications will be programmatically imputed from the original cohort if the medication is "ongoing" or if the end date is within 60 days prior to the screening visit date. Medication entries resulting from such imputation will be removed if an identical entry (preferred term, dose, start date) is present in the EDC.

Prior medications are defined as any medications which started prior to the first dose of XYWAV. Concomitant medications are defined as any medications with a stop date on or after the date of the first dose of XYWAV or any medication that is ongoing. A medication with completely missing use dates or partially missing use dates without evidence that the medication was stopped prior to the first dose of study drug will be considered a concomitant medication.

Prior and concomitant medications will be coded with the Anatomical Therapeutic Class (ATC) level 4 and preferred drug name using the World Health Organization (WHO) drug dictionary, version Mar 2024 or later. Unique medications will be summarized by ATC level 4 and preferred drug name using the Safety Set. A listing will also be presented.

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6.6. Protocol Deviations

Important protocol deviations as classified in the CTMS will be summarized type of deviation using the Enrolled Set. All protocol deviations will also be provided in a listing.

7. EFFECTIVENESS

Analysis of effectiveness endpoints will be performed separately for Narcolepsy, IH [REDACTED] cohorts.

Unless otherwise specified, effectiveness endpoints will be analyzed using the Completer Set.

7.1. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions asking the subjects how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing. The ESS total score is the sum of the 8 item-scores and range between 0 and 24. Higher scores indicate greater daytime sleepiness. If three or more item scores are missing at a specific time point, the ESS total score will be set to missing. If one or two ESS item scores are missing at a specific time point, the mean of the remaining seven or six non-missing ESS item scores at that time point will be used to impute the missing ESS item value. The ESS total score will be then calculated as the sum of the observed and imputed item scores.

The ESS total score at each visit with change from baseline will be summarized for all participants as continuous variables.

Least-squares mean change from baseline (LS-means), standard error (SE), 95% confidence interval, and p-value will be provided at the End of Treatment visit using an analysis of covariance (ANCOVA) model adjusted for the baseline value.

Example SAS Code for the ANCOVA model is shown below:

```
proc mixed data = DSET;
  class avisitn;
  where avisitn = [EOT];
  model chg = base avisitn;
  lsmeans avisitn;
run;
```

To assess the effect of early treatment discontinuation on the endpoint, analyses will be repeated using the Effectiveness Set.

7.2. Polysomnography (PSG)

Each participant's sleep architecture will be characterized by PSG during overnight study visits at Baseline and EoT. The PSG recordings will be obtained according to a standard protocol (with a standardized montage), procedures for biocalibrations and technician notations, and technical specifications as outlined in the study PSG Manual which will be provided to each study site.

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All PSG parameters and their changes from baseline will be summarized as continuous variables. for the following time periods: Full night (code F); first 4 hours (code F4); second 4 hours (code S4).

The primary analysis will use the full night summary (code F) to estimate least-squares mean change from baseline (LS-means), standard error (SE), 95% confidence intervals, and p-value using an analysis of covariance (ANCOVA) model adjusted for the baseline value.

Supplemental analyses will repeat the primary ANCOVA models for the first 4 hours summary (code F4) and second 4 hours summary (code S4).

Sensitivity analyses will be performed in which the primary ANCOVA models will be additionally adjusted for the change from baseline in nocturnal sleep time. The corresponding LS mean calculation will be estimated using the mean baseline value and setting the change in sleep period time to zero.

Correlations between ESS total score and PSG parameters at each visit and between change in ESS total score and change in PSG parameters will be conducted visually by scatterplots and analytically by Pearson and Spearman coefficients (with 95% confidence intervals).

PSG Endpoints

- Duration of sleep stages (Wake^{*}, REM^{*}, Stage 1^{*}, Stage 2^{*}, Stage 3^{†,*})
- Proportion of sleep stages (Wake^{*}, REM^{*}, Stage 1^{*}, Stage 2^{*}, Stage 3^{*})
- Sleep stage shifts (N1/N2/N3/REM to Wake or N2/N3/REM to N1)^{†,*}
- Total number of awakenings^{†,*}
- Total number of arousals^{*}
- Minimum oxygen saturation (during TIB)
- Mean oxygen saturation (during sleep)
- Apnea/Hypopnea Index
- Number of obstructive apneas
- Number of mixed apneas
- Number of central apneas
- Number of hypopneas
- Sleep onset latency
- Wake after sleep onset (WASO)
- REM sleep latency
- Total sleep time (TST)
- REM density
- Spectral frequency distribution

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- Alpha, beta, delta, sigma, and theta band measurements will be separately averaged across multiple channels and summarized for each non-REM sleep stage (N1, N2, N3)

[†]Endpoint is used in hierarchical statistical testing procedure (Section 5.3).

*To assess the effect of early treatment discontinuation on this endpoint, primary and supplemental analyses will be repeated using the Effectiveness Set.

7.3. Patient Global Impression of Change (PGI-C)

PGI-C is a self-administered instrument with 7-point Likert-type scale to measure a participant's impression of response to treatment. Using this scale, participants will be asked to rate their impression of change in sleep inertia, fatigue, and overall symptoms.

PGI-C responses will be aggregated as Improved (top 2 and top 3 levels), No Change, or Worsened (bottom 3 levels).

Categorical variable summaries of PGI-C and aggregated classifications will be reported for each symptom. Treating each response level as a numeric variable (valued 1-7), a continuous variable summary will also be reported for each symptom.

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

PGI-S is a self-administered instrument with 7-point Likert-type scale to measure a participant's severity of a condition. Using this scale, participants will be asked to rate the level of severity of each of sleep inertia, fatigue, and overall symptoms.

Categorical variable summaries of PGI-S and aggregated classifications will be reported for each symptom. Treating each response level as a numeric variable (valued 1-7), continuous variable summaries at each visit, including change from baseline, will also be reported for each symptom.

Crosstabulations and the McNemar-Bowker test will be performed to describe change in PGI-S responses between time points.

7.5. Sleep eDiary

The electronic Sleep Diary will include questions about the participant's nightly sleep patterns (e.g., sleep time, awakenings, wake time) and sleep quality, how rested/refreshed the participant feels upon awakening, caffeine use the prior day, and whether the night was atypical (e.g., a holiday).

At least 5 days of data are required during the 8-day assessment prior to the PSG Visits.

The parameters below will be derived from the Sleep eDiary:

- Nocturnal TST (NTST) = (Q6-Q2)-(Q3+Q5)
- Sleep Latency (SL) = Q3
- Time in Bed (TIB) = (Q6-Q1)
- Sleep Efficiency (SE) = NTST / TIB * 100
- Number of awakenings (NA) = Q4

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Parameters and their changes from baseline will be summarized as continuous or categorical variables, as appropriate.

For NTST, SL, TIB, SE, and NA parameters, participant mean score for the interval will be calculated by summing the parameters over all days and dividing by the number of days in which diaries were completed.

For NTST, least-squares mean change from baseline (LS-means), standard error (SE), 95% confidence interval, and p-value will be provided at each post-baseline time point using an analysis of covariance (ANCOVA) model adjusted for the baseline value.

7.6. Idiopathic Hypersomnia Severity Scale (IHSS) (IH only)

IHSS is a 14-item self-reported instrument that assesses the severity and functional consequences of IH symptoms. Questions capture symptoms of excessive sleepiness, sleep inertia, and long sleep duration. IHSS total scores range from 0 to 50.

IHSS total score is the sum of the fourteen item-scores. In addition, three component scores² will be analyzed (as exploratory endpoints): Daytime functioning (item 5 and items 9-14); sleep inertia (items 1-4 and item 8); and napping (items 6 and 7).

Imputation for missing items will be conducted as described:

If four or more item scores are missing at a specific time point, the IHSS total score and component scores will be set to missing. If fewer than four IHSS item scores are missing at a specific time point, then impute each missing item by multiplying the missing item's maximum response value by the average of the remaining non-missing items proportion of maximum response. Note that the maximum possible score can be either 3 or 4 depending on the specific question. The formula for imputation is as follows:

$$Q_j = M_j * \frac{\sum_i^n \frac{Q_i}{M_i}}{n}$$

$$T_{score} = \sum_i Q_i + \sum_j Q_j$$

Where: Qi = non-missing question item; Qj = missing question item; Mi = Maximum score of non-missing question item; Mj = Maximum score of missing question item; n = number of non-missing question items (n≥11); T_{score} = IHSS total score

IHSS total and component scores at each visit, and changes from baseline, will be summarized as continuous variables.

²Rassu, et al. J Clin Sleep Med 2022 Feb 1;18(2):617-629.

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Least-squares mean change from baseline (LS-means), standard error (SE), 95% confidence interval, and p-value will also be provided at each post-baseline time point using an analysis of covariance (ANCOVA) model adjusted for the baseline value.

7.7. Actigraphy

Actigraphy is a noninvasive tool to objectively measure activity profiles and is used to estimate sleep patterns based on validated algorithms. At least 5 days of wear are required during the 8-day assessment periods prior to the PSG Visits. Participants will be asked to wear the actigraphy device during the Baseline Assessment Period through Visit 2, and from SDP through Visit 4.

Actigraphy parameters are defined in a separate document which is incorporated by reference. Numerical measurements captured during each 24-hour period will be averaged across eligible days associated with each visit; categorical measurements will be represented as the modal response across eligible days associated with each visit. Aggregated values at each visit and changes from baseline will be summarized as continuous or categorical variables as appropriate.

7.8. Pre-PSG questionnaire values

The self-administered pre-PSG questionnaire, administered the night of PSG, includes questions about activities during that day (e.g., naps, any unusual events, caffeinated beverages) that may impact the PSG. Findings from the Pre-PSG questionnaire at each visit will be summarized as continuous or categorical variables, as appropriate.

7.9. Cataplexy attack frequency (NT1 only)

Participants will complete the Cataplexy eDiary every day during the Baseline and End of Treatment Assessment Periods, including during the PSG Visits, on their personal device or a device provided by a central vendor. At least 5 days of data are required during the 8-day assessment periods prior to the PSG Visits. The weekly rate of cataplexy attacks is derived as the average number of daily attacks from days with non-missing data within the week multiplied by seven. Weekly rate for each visit and change from baseline will be summarized as continuous variables.

7.10. Narcolepsy Severity Scale (NSS/NSS2; Narcolepsy only)

The NSS is a 15-item self-administered questionnaire (score: 0 to 57) that assesses the severity and consequences of the 5 major narcolepsy symptoms as daytime sleepiness (items 1-7), cataplexy (items 8-10), hallucinations (items 11-12), sleep paralysis (items 13-14), and disrupted nighttime sleep (item 15). A modified 12-item version omitting the questions about cataplexy will be used for participants with NT2 (NSS2); this version has a maximum score of 44.

For NSS items 1, 8, 9, 11, and 13 and for NSS2 items 1, 8, and 10: Responses are given in terms of episodes per week. Responses should be recoded using the following mapping (use the highest applicable code):

0. Never/no episodes during the past week
1. ≥ 1 episodes per week
2. ≥ 4 episodes per week

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3. ≥ 7 episodes per week
4. ≥ 10 episodes per week
5. ≥ 14 episodes per week

Presence of each the five narcolepsy symptoms (four, for NSS2) is defined by a positive answer (score ≥ 1) to at least one of the items related to that symptom. NSS/NSS2 total score is calculated as the sum of all item scores (recoded as necessary).

At each visit, counts of symptoms present, NSS/NSS2 total score, and changes from baseline will be summarized as continuous variables.

7.11. Orthostatic Hypotension Questionnaire (OHQ)

The OHQ is a validated 10-item self-administered questionnaire. The OHQ consists of 2 components: the Orthostatic Hypotension Symptom Assessment (OHSA), to measure the presence and severity of symptoms, and the Orthostatic Hypotension Daily Activity Scale (OHDAS), to measure the impact of orthostatic symptoms on daily activities.

- OHSA = sum (items 1 through 6)
- OHDAS = sum (items 7 through 10)
- OHQ Total Score = sum (OHSA score and OHDAS score)

The OHSA, OHDAS, and OHQ total score at each visit, and their changes from baseline, will be summarized as continuous variables.

7.12. Psychomotor Vigilance Test (PVT)

The PVT is a test used to measure the impact of sleep inertia on vigilant attention. It will be administered on the morning after each PSG visit at 10 minutes, 40, and 90 minutes after final (natural) awakening. Each PVT test is 10 minutes in duration. During the PVT, participants are instructed to respond, as quickly and accurately as possible, to a stimulus presented at random intervals of 2-10 seconds for the 10-minute duration of the task.

The number of lapses (reaction times >500 ms) during each PVT trial will be summarized as a continuous variable, and a nonlinear model will be constructed as follows:

$$y_{ijk}(t_{ijk}) = I_k e^{(-r_k \times t_{ijk})} + \alpha_{ik} + \varepsilon_{ijk}$$

where y =number of lapses, i =subject, j =within-visit measurement timepoints, and k =visit number; the time variable t is expressed in minutes since final awakening, α_{ik} is a subject-specific intercept (random effect) and ε_{ijk} is the error term.

As the variance of responses is expected to reduce over time, the model will assume a heteroskedastic error structure. Sensitivity analyses will be performed in which the model parameters are separately estimated assuming homoscedastic error structures in the original scale and in the logarithmic scale.

The model parameters of interest are I_k and r_k which represent the visit-specific magnitude of sleep inertia upon awakening and sleep inertia dissipation rate, respectively, as measured by the PVT. Nominal hypothesis tests will be performed for each parameter, comparing follow-up to

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baseline visit. Example SAS code to fit the model and perform the hypothesis tests is provided in Appendix 3.

Scatterplots will be constructed depicting observed time-response values at each assessment. The X-axis will denote time since awakening using a linear axis. Assessments are expected to be performed at approximately 10, 40, and 90 minutes after awakening. The Y-axis will denote the number of lapses. Separate lines will be drawn connecting the means (with bars denoting standard error) for each target assessment time at baseline and follow-up.

Additional parameters from each PVT assessment will be summarized as continuous variables.

- Number of false starts (responses before the appearance of a stimulus or coincidental reaction times <100 ms)
- Mean reaction time (RT) (RT_{mean})
- Mean response speed (mean reciprocal RT) ($[1/RT]_{\text{mean}}$)
- Log signal to noise ratio (LSNR; see Appendix 4 for calculation)³

7.13. Karolinska Sleepiness Scale (KSS)

The KSS is a 9-point Likert-type scale that measures subjective sleepiness at a particular time during the day. The KSS will be administered within approximately 2 minutes of the participant's final awakening and immediately before and after each of the PVT tests.

KSS responses will be summarized at each assessment as a continuous variable, and a nonlinear model will be constructed as follows⁴:

$$y_{ijk}(t_{ijk}) = I_k e^{(-r_k \times t_{ijk})} + \alpha_{ik} + \varepsilon_{ijk}$$

where y =KSS score, i =subject, j =within-visit measurement timepoints, and k =visit number; the time variable t is expressed in minutes since final awakening, α_{ik} is a subject-specific intercept (random effect) and ε_{ijk} is the error term.

As the variance of responses is expected to reduce over time, the model will assume a heteroskedastic error structure. Sensitivity analyses will be performed in which the model parameters are separately estimated assuming homoscedastic error structures in the original scale and in the logarithmic scale.

The model parameters of interest are I_k and r_k which represent the visit-specific magnitude of subjective sleepiness upon awakening and subjective sleepiness dissipation rate, respectively, as measured by the KSS. Nominal hypothesis tests will be performed for each parameter,

³Chavali VP, Riedy SM, Van Dongen HPA (2017). Signal-to-Noise Ratio in PVT performance as a cognitive measure of the effect of sleep deprivation on the fidelity of information processing. Sleep 40: zsx016.

⁴Lundholm KR, Honn KA, Skeiky L, Muck RA, Van Dongen HPA. Trait inter-individual differences in the magnitude of subjective sleepiness from sleep inertia. Clocks & Sleep, 2021; 3: 298–311.

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comparing follow-up to baseline visit. Example SAS code provided in Appendix 3, modified to accommodate additional time points, will be used to fit the model and perform the hypothesis tests.

Scatterplots will be constructed depicting observed time-response values at each assessment. The X-axis will denote time since awakening using a linear axis. Assessments are expected to be performed at approximately 0, 9, 21, 39, 51, 89, and 101 minutes after awakening. The Y-axis will denote the KSS score. Separate lines will be drawn connecting the means (with bars denoting standard error) for each target assessment time at baseline and follow-up.

7.14. Functional Outcomes of Sleep Questionnaire (FOSQ-10)

The FOSQ-10 is an instrument to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these activities are improved by effective treatment.

FOSQ-10 total score is calculated by first taking the mean of the items for each subscale with more than 1 item completed and then taking the mean across the non-missing 5 subscales (General Productivity, Activity Level, Vigilance, Social Outcomes, Intimacy and Sexual Relationship) multiplied by 5. Score range is 5–20 points, with higher scores indicating better functional status.

Missing responses, and responses from activities in which the respondent does not do that activity for other reasons are not included in the score calculation (i.e., not included in the calculation of average value for subscales). Therefore, missing responses do not necessarily prevent score calculation.

The FOSQ-10 total score and change from baseline will be summarized as continuous variables.

7.15. British Columbia Cognitive Complaints Inventory (BC-CCI)

The BC-CCI was developed to measure cognitive complaints in individuals with major depressive disorder (MDD). It is a 6-item self-report measure that asks respondents to rate problems with specific cognitive symptoms using a 4-point scale. The total score ranges from 0 to 18 by summing all items. Total score will be set to missing if any individual item is missing. Higher scores indicate greater severity of cognitive impairment.

The BC-CCI total score and change from baseline will be summarized as continuous variables. At each time point, results for the three supplemental questions will be summarized as categorical data and divided into categorical groupings. The groups are as follows by Cognitive Complaints: 0-4=none or minimal; 5-8=mild; 9-14=moderate; 15-18=severe.

7.16. Participant Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9-item scale of depressive symptoms developed based on the 9 diagnostics criteria for major depressive disorder in the DSM-IV. The PHQ-9 total score is the sum of 9 item-scores and can range between 0 and 27 with higher scores indicating greater severity of depression.

If 3 or more items are left unanswered, the total score will not be computed. If 1 or 2 items are left unanswered, a prorated score will be calculated. The prorated score is calculated as the sum

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of the scores of the items that were answered to get a partial raw score. Then, the partial raw score will be multiplied by the total number of items on the PHQ-9 (i.e., 9) and divided by the number of items that were actually answered (i.e., 7 or 8). If the result is a fraction, it will be rounded to the nearest whole number.

PHQ-9 total score at each visit and change from baseline will be summarized as continuous variables and divided into categorical groupings. The groups are as follows by Depression Severity: 0-4=none-minimal; 5-9=mild; 10-14=moderate; 15-19=moderately severe; 20-27=severe.

7.16.1. Participant Health Questionnaire-2 (PHQ-2)

PHQ-2, which is calculated as the sum of the first two PHQ-9 items, will also be summarized as a continuous variable at each visit with change from baseline.

7.17. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)

The self-administered WPAI:SHP is a 6-item questionnaire that measures work time missed and work and activity impairment because of a specified health problem. Questions related to work are answered by employed participants. All participants answer questions on activity impairment.

- Percent work time missed due to IH or narcolepsy: $\text{Score} = Q2 / (Q2 + Q4)$
- Percent impairment while working due to IH or narcolepsy: $\text{Score} = Q5/10$
- Percent overall work impairment due to IH or narcolepsy: $\text{Score} = Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))) \times (Q5/10)]$
- Percent activity impairment due to IH or narcolepsy: $\text{Score} = Q6/10$

WPAI values at each visit and change from baseline will be summarized as continuous variables.

8. SAFETY

Safety endpoints will be analyzed using the Washout Set or Safety Set and reported separately by cohort.

8.1. Exposure

8.1.1. Extent of Exposure

Exposure duration (in days) and total nightly dose (in g/night) will be summarized as continuous variables for the titration period, stable dose period, and entire intervention period.. Summaries for first dose, second dose (where prescribed), and total nightly dose will be provided. A frequency table displaying combinations of first dose and second dose during the stable dose period will also be provided.

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8.1.2. Treatment Compliance

XYWAV treatment compliance will be calculated as the ratio of treatment consumed divided by the expected consumption, expressed as a percentage:

$$\text{Compliance (\%)} = \frac{\text{Volume of solution taken during the intervention period}}{\text{Volume of solution that should have been taken during the intervention period}} \times 100\%$$

The numerator is the volume of solution taken during a study period (i.e., total dispensed – total returned). The denominator is the total daily volume that should have been taken during the intervention period according to the prescribed daily dose(s).

$$\text{Volume That Should Have Been Taken (ml)} = \text{Dose (g)} * 0.5 \text{ ml/g}$$

Study drug dispense records and study drug dosing records will be assigned to the [REDACTED] cohort starting on the first study drug dispense date on or after the V2 PSG overnight visit. Study drug dispenses and study drug dosing records prior to that date will be assigned to the Narcolepsy cohort.

Treatment compliance during the intervention period will be summarized as a continuous variable and summarized by category (<75%, 75-125% and >125%).

8.1.3. Clinician-Reported Dosing Form

Data captured on the Clinician-Reporting Dosing Form will be listed only.

8.2. Adverse Events

AEs will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 27.0 or later. The investigator will assess the relationship of each AE to study drug. AE with a missing relationship to study drug will be reported as related in the summaries. Severity, as determined by the Investigator using National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0 or higher, will be classed as mild, moderate, severe, life-threatening, or fatal. An AE with missing severity will be reported as missing in the summaries.

If a participant has multiple episodes of events coded to the same SOC or PT, then the participant will be counted just once in the summaries for that term. Participant incidence of AEs by SOC and PT tables are sorted by SOC (alphabetical order) and then by PTs (descending order) within each SOC for the overall frequency.

A summary of AEs with the number and percent of subjects who experienced the following types of events will be provided:

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- Subjects with any AE
- Subjects with AE by maximum severity
- Subjects with any AEs related to study intervention
- Subjects with any serious related AE
- Subjects with any AE leading to discontinuation
- Subjects with any AE leading to death

In addition, participant incidence of AEs will be summarized by following:

- SOC and PT
- Maximum severity by SOC and PT
- Treatment-related by SOC and PT
- AE leading to discontinuation by SOC and PT
- Serious AEs
- Fatal AEs

Separate summaries will be provided by cohort for AEs during the washout period (Narcolepsy and IH cohorts only) and during the treatment period.

8.3. Laboratory Assessments

Clinical laboratory assessments are detailed in Appendix 2 of the Protocol.

Hematology and Clinical Chemistry values at each scheduled visit with change from baseline will be summarized as continuous variables. Urinalysis values at each scheduled visit with change from baseline will be summarized as continuous or categorical variables as appropriate. Number and percent of participants with abnormal findings at each study visit, if any, will be summarized as categorical variables. Data listings will include all visits (scheduled and unscheduled) and annotations for abnormal results.

Serum or urine dipstick pregnancy, FSH and estradiol (where performed), breath alcohol, and urine drug screen results at screening and other visits (as necessary) will be listed only.

8.4. Vital Signs

8.4.1. Vital Signs Captured at Scheduled Study Visits

Vital sign values at each scheduled visit with change from baseline will be summarized as continuous variables and listed; listings will also include any values captured during unscheduled visits.

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8.4.2. Vital Signs Captured Within PK Visits

Vital signs and pulse oximetry values captured at scheduled time points during PK Visits, with change from pre-dose baseline (defined for each PK visit), will be summarized as continuous variables.

8.5. ECG

Local, machine-read ECG summary values at each visit with change from screening will be summarized as continuous variables. Summary variables collected include ventricular rate, PR interval, QRS duration, QT interval (including corrected versions), and RR interval.

Overall ECG assessment will be summarized categorically as Normal, Abnormal (not clinically significant), or Abnormal (clinically significant). Shift tables between screening/baseline and EOT will also be provided.

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

C-SSRS responses and aggregated responses for suicidal ideation or suicidal behavior will be summarized as categorical variables separately for screening visit and at each visit during follow-up.

9. PHARMACOKINETIC ANALYSES

Whole blood samples will be collected at prespecified timepoints as outlined in the protocol. Actual times of dose administration and blood samples for oxybate concentrations must be precisely recorded on the source document and in the eCRF. Blood samples will be processed to obtain plasma samples, which will be analyzed for oxybate concentrations using a validated bioanalytical method.

9.1. Pharmacokinetic Endpoints

PK will be evaluated using noncompartmental analysis as data permits. This section further describes the definition of the PK endpoints.

- C_{max} is defined as the maximum plasma drug concentration over post dose samples.
 - For the twice nightly regimen, C_{max1} is defined as the maximal concentration from post the 1st evening dose up to and including the 2nd evening pre-dose concentration. C_{max2} is defined as the maximal concentration post 2nd evening dosing. Overall C_{max} is defined as the highest observed concentration during the 8-hour sampling period post the first nightly dose.
 - For once nightly, C_{max} is defined as the maximum plasma drug concentration during the 8-hour sampling period post dose.
- T_{max} is defined as the elapsed time from administering the dose to the maximum drug concentration, measured in hours. Values are calculated for the following:
 - For the twice nightly regimen, T_{max1} is time to C_{max1} . T_{max2} is time to C_{max2} . Overall T_{max} is the time to reach the overall C_{max} .

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- AUC is defined as the area under the plasma concentration versus time curve as calculated by the linear trapezoidal method for the following intervals
 - For the twice nightly regimen, AUC₁ for the first dosing interval (using samples from initial dose to 2nd evening pre-dose) and AUC₂ for the second dosing interval (using samples post 2nd dose), AUC_t is the total AUC following both nightly doses where *t* refers to the last measurable plasma concentration. AUC_∞ is the sum of and AUC_t + AUC_{t-∞} (i.e. C_{last} / elimination rate constant) if data permit.
 - Scheduled pre-dose samples will have 0 used for the elapsed time from dosing for calculation of AUC values.
- t_{1/2} is defined as the terminal half-life and is based on a minimal of 3 last plasma concentrations in the terminal phase of the concentration-time profile if data permit.

9.2. Pharmacokinetic Analyses

Descriptive statistics including number of subjects, mean, SD, minimum, median, maximum, coefficient of variation, geometric mean, and geometric SD will be used to summarize concentration data and PK parameters for subjects based on dose regimens having N ≥ 3.

In calculation of the concentration summaries and for the calculation of PK parameters, if concentration values are below the limit of quantitation (BLQ), they will be set to zero. Subjects who are included in the PK summary but have missing data for a particular PK parameter will not be included in the analysis for that endpoint. Unused data, measurements from excluded subjects, unscheduled collections, or extra measurements will not be included in the summaries but will be presented in the participant listings.

For dose regimens having N ≥ 3, plasma oxybate concentration-time data will be graphically displayed as individual and as mean (SD) using linear and log scales.

Evidence of dose proportionality for C_{max} (for equally divided dose regimens only) and/or C_{max,1} (for equally or unequally divided dose regimens) will be investigated using the power model.

Specifically, $\ln(\text{PK parameter}) = \beta_0 + [\beta_1 \cdot \ln(\text{dose})]$

where β_0 is the intercept and β_1 is the slope for AUC_t, dose will be included as total nightly dose.

Dose proportionality is declared when the 90% CI for β_1 lies completely within the critical region defined as:

$$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta_1 < 1 + \frac{\ln(\theta_H)}{\ln(r)}$$

where *r* represents the dose ratio between the minimum and maximum dose, $\theta_L = 0.8$, and $\theta_H = 1.25$.

Listings will summarize the dose regimen, oxybate concentration-time data by scheduled and actual sampling times, PK parameters, last meal and/or snack time.

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10. PHARMACODYNAMIC ANALYSES

Not Applicable

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11. MODIFICATION HISTORY

Version	Date	Description
2.0	09 SEP 2024	<p>General revisions to align with recent protocol amendments.</p> <p>Correction to PSG parameter and cut point used for IH long- vs non-long sleep subgroup assignment. Updated reference footnote.</p> <p>Removed references to repeated measures ANCOVA because only change from Baseline to End of Treatment will be estimated.</p> <p>Sleep eDiary, cataplexy diary, and actigraphy data requirement reduced to 5 days from 7 days.</p> <p>Correction to sleep diary Nocturnal Awakenings variable type from categorical to continuous.</p> <p>Added exposure summaries for titration and stable dose periods, first and second dose, and combinations of first and second dose.</p> <p>Clarified study day calculations and visit/period/epoch assignment for assessments conducted during overnight PSG/PK visits.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Clarified which protocol deviations are summarized in output table.</p> <p>[REDACTED]</p> <p>Clarified allocation of treatment compliance data between Narcolepsy [REDACTED] cohort [REDACTED].</p> <p>Included listing for Clinician-Reported Dosing Form.</p>

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		<p>Removed PGIs scatterplots.</p> <p>Corrected description of PVT plots to use mean and standard error.</p> <p>Provided additional details for calculating NSS/NSS2.</p> <p>Corrected equation for Sleep Efficiency to express result as percentage.</p> <p>Added a Washout Set for reporting adverse events occurring during that period.</p> <p>Added details regarding PSG spectral frequency analysis.</p> <p>Added details for presentation of PVT and KSS scatterplots.</p> <p>Removed description for scatterplots of change in PGIs vs PGlc as this will not be included in the final report.</p>
1.0	16 FEB 2024	Initial Version

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Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse event
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	AUC_t Area under the concentration-time curve from time zero to last measurable concentration
BC-CCI	British Columbia Cognitive Complaints Inventory
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CL	Drug clearance
C_{max}	Maximum plasma concentration
CRF/eCRF	Case report form/Electronic case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECG	Electrocardiogram/Electrocardiography
ED	Early Discontinuation (Visit)
eDiary	Electronic diary
EDS	Excessive daytime sleepiness
EoT	End of Treatment (Intervention)
FOSQ-10	Functional Outcomes of Sleep Questionnaire-10
ICF	Informed consent form
IH	Idiopathic Hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale
KSS	Karolinska Sleepiness Scale
NA	Not applicable
NSS	Narcolepsy Severity Scale
NT1	Type 1 Narcolepsy
OHQ	Orthostatic Hypotension Questionnaire

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PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Participant Health Questionnaire
PK	Pharmacokinetic(s)
PRO	Participant-reported outcome
PSG	Polysomnography
PVT	Psychomotor Vigilance Test
REM	Rapid eye movement
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
TST	Total sleep time
WASO	Wakefulness after sleep onset
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem

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Appendix 1: Adverse Event Date Imputation Rules

Missing AE start dates will be imputed in the AdaM datasets for AE. However, missing AE end dates will not be imputed. After imputation based on rules below, if the imputed AE start date is after the AE end date, the start date will be imputed by the AE end date further.

Incomplete Adverse Event Onset Date

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

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Appendix 2: Prior/Concomitant Medications Date Imputation Rules

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

Do not impute if Ongoing Flag is checked.

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

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Appendix 3: Example SAS code for PVT and KSS models

```

/* Primary: Heteroskedasticity on original scale, variance proportional to mean */
proc nlmixed data = example gconv = 0;
  parms I1 = 40 dI = 0 r1 = 10 dr = 0 a1 = 8 da = 0 s2a = 2 varpct = 50;
  bounds I1 > 0, r1 > 0, a1 > 0;
  I = I1 + (k=2) * dI;
  r = r1 / 10 + (k=2) * dr / 10;
  a = a1 + (k=2) * da;
  pred = I * exp(-r*t) + a + vara;
  varerr = (pred * (varpct / 100));
  model y ~ normal(pred, varerr);
  random vara ~ normal(0, s2a) subject=i;
  estimate "I1" I1;
  estimate "I2" I1+dI;
  estimate "H0: I1=I2" dI;
  estimate "tau1" 10/r1;
  estimate "tau2" 10/(r1+dr);
  estimate "H0: tau1=tau2" 10/r1-10/(r1+dr);
  estimate "Predicted mean of t(Pre, &Time1.)" I1 * exp(-(r1/10)*&Time1.) + a1;
  estimate "Predicted mean of t(Pre, &Time2.)" I1 * exp(-(r1/10)*&Time2.) + a1;
  estimate "Predicted mean of t(Pre, &Time3.)" I1 * exp(-(r1/10)*&Time3.) + a1;
  estimate "Predicted mean of t(Post, &Time1.)" (I1+dI) * exp(-((r1+dr)/10)*&Time1.) + a1 + da;
  estimate "Predicted mean of t(Post, &Time2.)" (I1+dI) * exp(-((r1+dr)/10)*&Time2.) + a1 + da;
  estimate "Predicted mean of t(Post, &Time3.)" (I1+dI) * exp(-((r1+dr)/10)*&Time3.) + a1 + da;
  estimate "SD(Pre, &Time1.)" sqrt(I1 * exp(-(r1/10)*&Time1.) + a1) * sqrt(varpct/100);
  estimate "SD(Pre, &Time2.)" sqrt(I1 * exp(-(r1/10)*&Time2.) + a1) * sqrt(varpct/100);
  estimate "SD(Pre, &Time3.)" sqrt(I1 * exp(-(r1/10)*&Time3.) + a1) * sqrt(varpct/100);
  estimate "SD(Post, &Time1.)" sqrt((I1+dI) * exp(-((r1+dr)/10)*&Time1.) + a1 + da) * sqrt(varpct/100);
  estimate "SD(Post, &Time2.)" sqrt((I1+dI) * exp(-((r1+dr)/10)*&Time2.) + a1 + da) * sqrt(varpct/100);
  estimate "SD(Post, &Time3.)" sqrt((I1+dI) * exp(-((r1+dr)/10)*&Time3.) + a1 + da) * sqrt(varpct/100);
run;

/* Sensitivity: Homoskedasticity on original scale */
proc nlmixed data = example gconv = 0;
  parms I1 = 40 dI = 0 r1 = 10 dr = 0 a1 = 8 da = 0 s2a = 2;
  bounds I1 > 0, r1 > 0, a1 > 0;
  I = I1 + (k=2) * dI;
  r = r1 / 10 + (k=2) * dr / 10;
  a = a1 + (k=2) * da;
  pred = I * exp(-r*t) + a + vara;

```

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```

model y ~ normal(pred, varerr);
random vara ~ normal(0, s2a) subject=I;
estimate "I1" I1;
estimate "I2" I1+dI;
estimate "H0: I1=I2" dI;
estimate "tau1" 10/r1;
estimate "tau2" 10/(r1+dr);
estimate "H0: tau1=tau2" 10 / r1 - 10 / (r1 + dr);

run;

/* Sensitivity: Homoskedasticity on log scale */
proc nlmixed data = example gconv = 0;
parms I1 = 40 dI = 0 r1 = 10 dr = 0 a1 = 8 da = 0 s2a = 20;
I = I1 + (k=2) * dI;
r = r1 / 10 + (k=2) * dr / 10;
a = a1 + (k=2) * da;
pred=I * exp(-r*t) + a + vara;
model logy ~ normal(log(pred), varerr);
random vara ~ normal(0, s2a) subject=i;
estimate "I1" I1;
estimate "I2" I1 + dI;
estimate "H0: I1=I2" dI;
estimate "tau1" 10 / r1;
estimate "tau2" 10 / (r1 + dr);
estimate "H0: tau1=tau2" 10 / r1 - 10 / (r1 + dr);

run;

```

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Appendix 4: Calculation for PVT LSNR

$$SNR \approx \frac{N(\sum_{i=1}^N w_i S_i)^2}{\sum_{i=1}^N [w_i (S_i \sum_{i=1}^N w_i - \sum_{i=1}^N w_i S_i)^2]} + 1$$

where $S_i = 1 / (RT_i - C)$, $w_i = 1 / (r^2 S_i + 1)$, $C = 100$ ms, $r^2 = 196$ ms, RT_i is the i th RT (in ms), and N is the number of trials in the PVT session. False starts (i.e., trials with responses prior to 150 ms after stimulus onset) are not included.

$$LSNR = 10 \log_{10}(SNR)$$

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Envelope Sent	Hashed/Encrypted	9/9/2024 1:08:05 PM
Certified Delivered	Security Checked	9/9/2024 1:12:21 PM
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