STATISTICAL ANALYSIS PLAN

VERSION: 3.0
DATE: 05-DEC-2024

STUDY DRUG:

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

PROTOCOL/STUDY NUMBER:

JZP258-406-04 (Amendment 4: 17 May 2024)

STUDY TITLE:

An Open-Label, Multicenter Switch Study Evaluating Changes in Blood Pressure in Participants With Narcolepsy Switching From High-Sodium Oxybate to XYWAV

SPONSOR:

Jazz Pharmaceuticals, Inc.

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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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 JZP258-406; the current version is based on Protocol v4.0 dated 17 May 2024. Additional analyses or substantial revisions from the analyses outlined in this plan will be documented with rationale in the final CSR.

JZP258-406 is a Phase 3/Phase 4, multicenter, single-arm, open-label switch study. The study will enroll individuals diagnosed with Type 1 or Type 2 narcolepsy [redacted].

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution was developed as an alternative, low-sodium formulation of XYREM (high sodium oxybate) and contains the same active moiety, oxybate (GHB), as XYREM. By formulating oxybate with a mixture of cations, XYWAV has 92% less sodium than XYREM in the anticipated dose range of 6 to 9 g nightly.

The aim of this study is to quantify the change in 24-hour average SBP when participants with narcolepsy treated with high-sodium oxybate are transitioned to XYWAV. It is hypothesized that there will be a clinically relevant reduction of SBP after switching from high-sodium oxybate to XYWAV. The results of this study are anticipated to provide healthcare providers, patients, and payers with important new information regarding BP changes related to differences in sodium content between available oxybates for the treatment of narcolepsy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Efficacy Objective(s)

- Evaluate the impact of switching from high-sodium oxybate to XYWAV on 24-hour ambulatory SBP for participants with narcolepsy.

2.1.2. Secondary Efficacy Objective(s)

- Evaluate the impact of switching from high-sodium oxybate to XYWAV on daytime ambulatory SBP for participants with narcolepsy
- Evaluate the impact of switching from high-sodium oxybate to XYWAV on seated resting SBP for participants with narcolepsy
- Evaluate the impact of switching from high-sodium oxybate to XYWAV on nighttime SBP for participants with narcolepsy.

2.1.3. Exploratory Efficacy Objective(s)

- Evaluate the impact of switching from high-sodium oxybate to XYWAV on ambulatory DBP for participants with narcolepsy;
- Evaluate the impact of switching from high-sodium oxybate to XYWAV on seated resting DBP for participants with narcolepsy;

- Evaluate the impact of switching from high-sodium oxybate to XYWAV on daytime-nighttime DBP decline (dipping) in participants with narcolepsy;
- Evaluate the relationship between BP and urine sodium excretion;
- Evaluate the impact of switching from high-sodium oxybate to XYWAV on participant-reported change in conditions in participants with narcolepsy;
- Evaluate the impact of switching from high-sodium oxybate to XYWAV on participant-reported severity of conditions in participants with narcolepsy;

2.1.4. Safety Objective

- Evaluate safety in participants switching from high-sodium oxybate to XYWAV.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Change from baseline to EOT Visit on the 24-hour average SBP (mm Hg)

2.2.2. Secondary Endpoints

- Change from baseline to EOT Visit on the daytime average SBP (mm Hg)
- Change from baseline to EOT Visit on the seated resting average SBP (mm Hg)
- Change from baseline to EOT visit on nighttime average SBP (mm Hg)

2.2.3. Exploratory Endpoints

[redacted]

2.2.4. Safety Endpoints

- Overall TEAEs
- TEAEs by maximum severity
- TEAEs related to study intervention
- Serious TEAEs
- TEAEs leading to discontinuation
- Fatal TEAEs

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 3/Phase 4, multicenter, single-arm, open-label switch study. In regions where XYWAV follows approved label, the study is a Phase 4 interventional study, and in regions where XYWAV does not follow approved label, the study is a Phase 3 study. The study will enroll patients with Type 1 or Type 2 narcolepsy [redacted].

To establish adequate exposure to high-sodium oxybate and well-tolerated treatment regimen, participants will be required to be on 6 to 9 g/night of high-sodium oxybate for at least 6 consecutive weeks before screening. After all other eligibility criteria have been assessed (except for clinical laboratory results obtained at screening), the 24-hour BP recording can be initiated, and the 24-hour urine collection obtained as baseline.

After all screening assessments have been completed, eligible participants will switch, on a gram-for-gram basis, from high-sodium oxybate (e.g., XYREM) to XYWAV. This switch must occur no more than 2 weeks after the 24-hour ambulatory BP recording.

After approximately 6 weeks of treatment with XYWAV, the 24-hour BP recording and 24-hour urine collection, along with other measurements will be repeated during the EOT Visit.

Study participation will end following a Safety Follow-Up Visit.

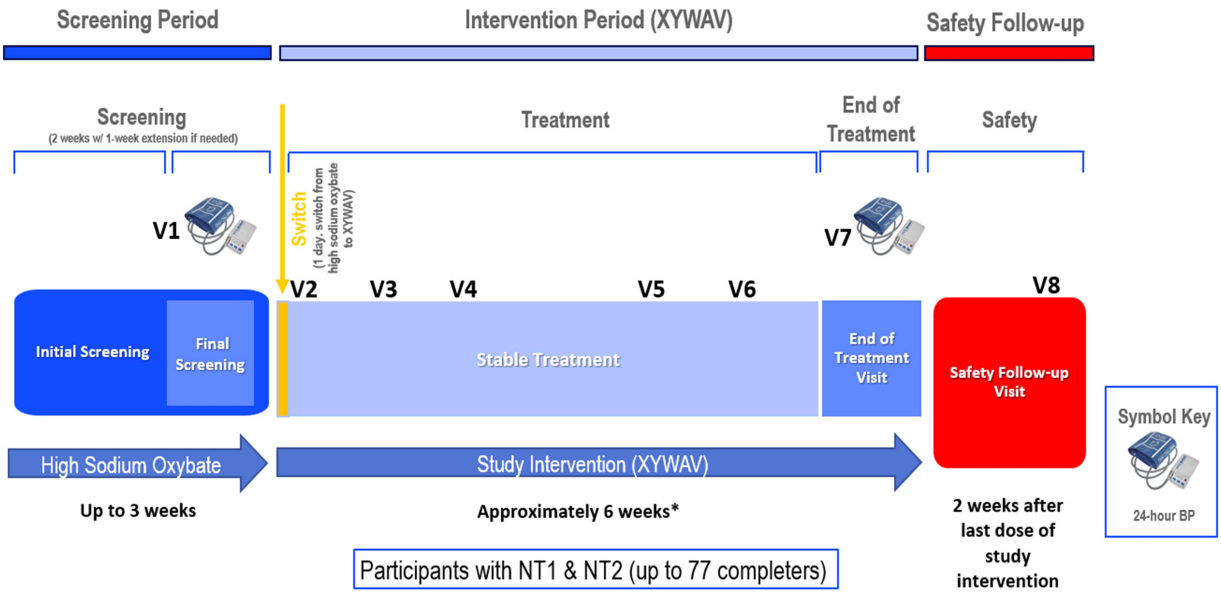
3.2. Study Treatment

The study duration for each participant will be up to approximately 11 weeks. The study includes the following study periods:

- A Screening Period (up to 3 weeks): All subjects will be evaluated for eligibility during the screening period, which will occur over a period of up to 3 weeks.

- An Intervention Period (approximately 6 weeks): this period is initiated by the switch from 6 to 9 g/night of high-sodium oxybate to the same (gram-per-gram) dose of XYWAV and includes approximately 6 weeks of treatment with the study intervention (XYWAV) and an EOT Visit.
  - Participants will continue taking study intervention until the EOT 24-hour BP recording meets minimum data quality standards. If needed, participants may repeat the EOT 24-hour BP recording up to 2 additional times, which would increase the duration of the Intervention Period and, consequently, the overall duration of study participation.
  - After completing an EOT 24-hour BP recording that meets minimum data quality standards, participants may transition to commercial XYWAV (as permitted by local health authorities) or other standard of care per physician discretion.
- A Safety Follow-up Visit (to be scheduled at least 14 days after the last dose of study intervention).

In this study, given the effects of some concomitant medicines on BP, participants who take stimulants and/or alerting agents or other medications known to affect BP are required to maintain doses unchanged from at least 2 months before study entry to the end of the study; participants who take antihypertensives at study entry must agree to maintain their treatment at the same dose throughout the study unless otherwise advised by their medical care provider. Any changes to these therapies during the study will be reported.



3.3. Power and Sample Size Considerations

There are no historical data on 24-hour average BP changes in participants switching from high-sodium oxybate to XYWAV. Given the limited information, data from other studies with drugs similar to oxybate were leveraged to inform the design of this study. It was determined that an

effect size of 3.0 or 3.5 with a SD range from 7.0 to 8.0 will be considered for power and sample size calculations. Sample sizes for different scenarios (different effect sizes and SD) were calculated with a one-sided significance level of 0.025 (Table 2).

A preselected target sample size of 57 will provide 90% power to detect a mean 24-hour average SBP difference of 3.5 mm Hg between baseline and the EOT Visit after switching from high-sodium oxybate to XYWAV for 6 weeks, assuming an SD of 8.0 points.

This study will use a 2-stage group sequential design in which the final sample size may be adaptively determined. The primary endpoint will be evaluated at a planned interim analysis, with the option to terminate enrollment if the primary endpoint is met, or to adaptively modify the final study sample size if the primary endpoint is not met (see Section 3.5).

Assuming a 15% discontinuation/withdrawal rate during the Intervention Period, a minimum of 67 (up to approximately 91) participants will be recruited to initiate the switch to XYWAV and to capture complete data. Assuming a 60% screen failure rate during the Screening Period, a minimum of 170 (up to approximately 230) study participants will be enrolled (sign the ICF) into the study.

Table 2. Power and Sample Size Calculations

Effect Size	Standard Deviation	80% Power	85% Power	90% Power
3.0	7.0	45	51	60
3.5	7.0	34	38	44
3.0	7.5	52	59	68
3.5	7.5	39	44	51
3.0	8.0	58	66	**77**
3.5	8.0	43	49	**57**

3.4. Randomization and Blinding

This is an open-label study with no randomization or blinding.

3.5. Interim Analysis

The interim analysis will be performed after 43 participants (75%) have completed the study. Using the sample size assumptions described in Section 3.3, the calculated O'Brien-Fleming one-sided alpha levels for statistical significance are 0.00998 for the interim analysis and 0.02194 for the final analysis. If the primary endpoint is not rejected at the interim analysis, the final sample size will be adaptively determined based on conditional power.

Conditional power refers to the probability of reaching statistical significance at the final analysis given the data obtained at the interim analysis, and it is calculated according to equation (1):

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

Where:

$\Phi(\bullet)$ is the standard normal cumulative distribution function

n_1 = actual sample size at interim analysis (expected to be n_1 = 43)

n_2 = planned sample size at final analysis (i.e., n_2 = 57)

$\tilde{n}_2$ = sample size increment between interim and planned final analyses (expected to be $\tilde{n}_2$ = 14)

z_α = the standard normal value for a type I error rate of α; i.e. Φ(1-0.025)=1.95996

$z_1 = \bar{x}_1 \,/\, se(\bar{x}_1)$, the z-statistic for 24-hour SBP change from baseline computed at interim analysis

Given the conditional power, the final sample size target will then be determined using a "promising zone" approach:

- If CP ≥90% (Favorable zone): Continue enrolling more participants until prespecified target sample size (N = 57).
- If CP <40% (Unfavorable zone): Continue enrolling more participants until prespecified target sample size (N = 57).
- If 40%≤CP<90% (Promising zone): Calculate additional sample size $\tilde{n}_2'$ based on formula (2). The final sample size target will be adjusted to $min(77, n_1 + \tilde{n}_2')$.

$$\tilde{n}_2' = \left(\frac{n_1}{z_1^2}\right)\left[\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{n_2 - n_1}} + z_\beta\right]^2 \qquad (2)$$

Where:

n_1 = actual sample size at interim analysis (expected to be n_1 = 43)

n_2 = planned sample size at final analysis (i.e., n_2 = 57)

z_α = the standard normal value for a type I error rate of α; i.e. Φ(1-0.025)=1.95996

z_β = the standard normal value for a type II error rate of β; i.e. Φ(1-0.10)=1.28155

$z_1 = \bar{x}_1 \,/\, se(\bar{x}_1)$, the z-statistic for 24-hour SBP change from baseline computed at interim analysis

Mehta and Pocock[1] reviewed the methodology demonstrating that the promising zone adaptive design maintains the type I error probability if the sample size is increased only when the conditional power falls into the promising zone.

Enrollment may continue while the interim analysis is being performed. To mitigate the risk of enrolling more participants than needed (i.e., "overruns"), the interim analysis will be based on the primary endpoint only, which will shorten the time needed to perform the analysis. However, all participants meeting analysis set criteria will be analyzed, regardless of the final sample size target.

[1]Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011 Dec 10;30(28):3267-84.

4. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Analysis Set	Description
Enrolled Set	The Enrolled Analysis Set will include all participants who provide informed consent for this study. This analysis set will be used to summarize participant disposition, protocol deviations (as classified in Clinical Trial Management Software), and inclusion/exclusion from the Safety Set, including reasons for exclusion from it.
Safety Set	All participants who take/receive at least 1 dose of study intervention (XYWAV). This analysis set will be used for reporting analyses of safety endpoints.
Completer Set	All participants who complete the EOT Visit after 6 weeks of study intervention with a 24-hour BP recording at this visit that meets the minimal data standards. This analysis set will be used for primary analyses of effectiveness endpoints.
Effectiveness Set	All participants who complete at least one post-baseline study effectiveness assessment (including early discontinuation). This analysis set will be used for reporting sensitivity analyses of effectiveness 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

All study data will be summarized using descriptive statistics. 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. Baseline and Study Day Definitions

5.2.1. Baseline

In this study, the screening period includes all measurements taken after informed consent is obtained until Day 1. Baseline refers to the most recent observation prior to Day 1.

5.2.2. Study Day

Day 1 is defined as the first day of interventional XYWAV use. Study day will be calculated as:

Study Day = (date of assessment – date of first dose of XYWAV) + 1

The intervention period extends from Day 1 until end of XYWAV.

5.2.3. Visit Windows

Listings will include all recorded assessments.

Unless otherwise specified, all data will be summarized using the CRF visit at which the data was collected. If a participant early discontinues, an ED Visit should be conducted as soon as possible after last study dose of XYWAV (or preferably while still on treatment).

Unscheduled visits in general will excluded from analyses where the corresponding scheduled visit is present. Unscheduled visits will only be mapped to a scheduled visit if the scheduled visit record is missing. If more than one unscheduled visit can be mapped to a visit window, the one with the assessment date closest to the target study day will be selected. If two visits are equally close to the target day (but on different sides), the later visit will be mapped.

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 latest one will be used in the analysis.
- If two observations are equidistant from the scheduled period day, then the observation with the latest collection date will be used in the analysis.
- If two 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.

Table 3: Visit Windows for Assessments or Measurements

Study Period	Study Visit	Target Study Day
Screening, Baseline	Visit 1	-21 to -1
Intervention	Visit 2	1
Intervention	Visit 3	7 ± 3

Intervention	Visit 4	14 ± 3
Intervention	Visit 5	28 ± 3
Intervention	Visit 6	35 ± 3
Intervention	Visit 7	42 ± 3
Follow-up	Visit 8	56 + 3

5.2.4. 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 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.

ABPM-based endpoints are subject to ABPM data adequacy criteria, defined in a separate specification document which is incorporated by reference. Device-provided summaries marked as "Valid" or "Valid Within Acceptable Limits" shall be eligible for analysis. If satisfactory data are not acquired on initial attempt, repeated 24-hour ambulatory measurements are permitted per protocol. If valid sleep diary entries covering the ABPM period are not available, the weekly mean sleep/wake time described in Section 8.1.3 may be used for creating the daytime/nighttime windows (Section 7.2.2).

5.3. Hypothesis Testing

The primary statistical hypothesis for this study is that there will be a clinically relevant decrease in 24-hour average SBP, compared to baseline, after switching from high-sodium oxybate to XYWAV for 6 weeks. The null and alternative hypotheses for the primary endpoint are:

$$H_0: \Delta_{SBP} = 0; H_1: \Delta_{SBP} < 0$$

Similarly defined hypotheses will be tested for the secondary endpoints of change in daytime and nighttime average SBP (both assessed using 24-hour ambulatory BP monitors) and change in seated resting SBP (assessed using the measurements performed by the site personnel).

5.4. Level of Significance & Multiplicity Adjustment

To control family-wise error rate inflation due to multiple endpoints and the interim analysis (Section 3.5), a fixed hierarchical testing sequence will be employed[2]. Testing begins with the first endpoint at the specified alpha level and continues through the sequence until an endpoint is not statistically significant. Remaining analyses will be considered exploratory and associated p-values will be considered nominal.

The Type I error rate for study endpoints will be set at a one-sided level of 0.025. To account for the possibility of ending the study at the interim analysis, statistical significance for the primary endpoint (#1) will be assessed using O'Brien-Fleming one-sided alpha levels of 0.00998 for the interim analysis and 0.02194 for the final analysis. Statistical significance for each of the secondary endpoints (#2 to #4) will be assessed using the Pocock one-sided alpha level of 0.0168 at either the interim or final analysis.

Statistical hypotheses to be tested (in sequential order):

1. Change in the 24-hour average SBP (mm Hg) following 6 weeks of XYWAV treatment after switching from high-sodium oxybate in participants with narcolepsy
2. Change in the daytime average SBP (mm Hg) following 6 weeks of XYWAV treatment after switching from high-sodium oxybate in participants with narcolepsy
3. Change in the seated resting average SBP (mm Hg) following 6 weeks of XYWAV treatment after switching from high-sodium oxybate in participants with narcolepsy
4. Change in the nighttime average SBP (mm Hg) following 6 weeks of XYWAV treatment after switching from high-sodium oxybate in participants with narcolepsy

Analyses not part of this hierarchy will be considered exploratory, and no multiplicity adjustment will be performed. P-values reported in standard table outputs will be considered nominal.

5.5. Subgroups and Subgroup Analyses

Summary output tables will report results overall and within narcolepsy subtype. Additional subgroup analyses may be conducted on the primary and key secondary efficacy endpoints for the following:

- Baseline use of antihypertensive medication
- Source of enrollment (traditional site-based vs. decentralized)
- Geographic region

[2]Multiple Endpoints in Clinical Trials. 2017; Available from: https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf

5.6. Changes to Planned Analyses

N/A

6. STUDY POPULATION SUMMARIES

6.1. Enrollment

The total number and percentage of participants for each Analysis Set defined in Section 4 will be summarized. The number of participants who enrolled by country and study site/investigator will be summarized.

6.2. Subject 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, received at least one dose, completed, are still ongoing (for interim analyses), and early discontinuation will be presented using the enrolled analysis set. Reasons 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 variables and other baseline characteristics will be summarized using descriptive statistics separately for Safety Set and Completer 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.

Surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 26.0 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.

- Prior medications are defined as any medications which started prior to the first dose of XYWAV.
- Concomitant medications will be defined as any medications with a stop date on or after the first conversion from Xyrem to XYWAV, during the study, 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 2022 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.

Hypertension medications (based on ATC Level 3) will be summarized:

- C02 – Antihypertensives
- C03 – Diuretics
- C07 – Beta blocking agents
- C08 – Calcium channel blockers
- C09 – Agents acting on the renin-angiotensin system

Other prior and concomitant medications will be reviewed by a medical panel for potential BP-modifying activity and will be classified accordingly for use in post hoc analyses.

6.6. Protocol Deviations

Major protocol deviations as classified in the CTMS will be summarized across the study period by deviation type using the Enrolled Analysis Set. All protocol deviations will also be listed.

7. EFFICACY

7.1. Primary Efficacy Endpoints and Analyses

The primary endpoint is the change in 24-hour ambulatory SBP from baseline to EOT Visit after switching from high-sodium oxybate to XYWAV for participants with narcolepsy. Only ABPM results denoted as "Valid" or "Valid within Acceptable Limits" may be used for analysis. "Invalid" results may be repeated as per protocol.

7.1.1. Primary Analysis

An analysis of covariance (ANCOVA) model will be used to estimate the primary efficacy endpoint using the SAS PROC MIXED procedure on the Completer Set. The model will include the change in 24-hour SBP from baseline to EOT Visit as the dependent variable and the mean-centered baseline 24-hour SBP as an independent variable in the model.

$$\text{BASE\_CENTERED} = \text{BASE} - \overline{BASE}$$

Example SAS Code for the ANCOVA model[3] is shown below:

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

Least-squares mean change from baseline (LS-mean), standard error (SE), 95% confidence interval, and *p*-value will be reported. Unadjusted values at each visit, including change from baseline, will also be summarized as continuous variables.

7.1.2. Sensitivity Analyses

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

7.1.3. Subgroup Analyses

To assess endpoint differences according to potential effect-modifying covariates, additional analyses for subgroups specified in Section 5.5 will be performed using the Completer Set.

Least-squares mean change from baseline (LS-means) and standard error (SE) will be provided for each subgroup. A nominal *p*-value will also be provided. Unadjusted values at each visit for each subgroup, including change from baseline, will also be summarized as continuous variables.

Example SAS Code for the ANCOVA model for subgroup analyses is shown below.

```
proc mixed data = DSET;
      class SUBG;
      model chg = base_centered SUBG /s cl;
      lsmeans SUBG / cl;
run;
```

7.2. Secondary Efficacy Endpoints and Analyses

For daytime/nighttime endpoints, only ABPM results denoted as "Valid" or "Valid within Acceptable Limits" may be used for analysis. "Invalid" results may be repeated as per protocol.

7.2.1. Primary Analysis

The secondary efficacy endpoints will be summarized and analyzed using the Completer Set and methods described for the primary endpoint.

[3]As the endpoint is only captured once during follow-up, including the constant-valued visit identifier (AVISITN) as a class covariate will not affect the model while permitting use of the LSMEANS statement to calculate the mean change in SBP.

Daytime and nighttime windows "are best defined using sleeping times reported by individual users' diary cards"[4]. Accordingly, day/night windows subdividing the 24-hour ABPM data will be defined using on sleep/wake times captured from participant sleep diary entries on the nights where the ABPM is being used. Sleep diary times may be converted to 12- or 24-hour format as necessary to merge with ABPM entries and perform the summaries. If valid sleep diary entries covering the ABPM night are not available but other diary entries for the visit are available, the weekly mean sleep/wake time (see Section 8.1.3) may be used to create the daytime/nighttime windows (Section 5.2.4).

A supporting analysis of the daytime/nighttime SBP endpoints will be performed using fixed time windows of 09:00h to 21:00h (daytime) and 01:00h to 06:00h (nighttime) for all participants[4,5]. However, if the percentage of participants with non-missing sleep diary data is below 85% (N<37 at the interim analysis; N<49 to N<66 at the final analysis), then the fixed window analysis will be considered the primary analysis (including use for statistical testing hierarchy) and the diary-based analysis will be considered supportive.

7.2.2. Sensitivity Analyses

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

7.2.3. Subgroup Analyses

To assess endpoint differences according to potential effect-modifying covariates, additional analyses for subgroups specified in Section 5.5 will be performed using the Completer Set and methods described for the primary endpoint.

7.3. Exploratory Endpoints and Analyses

[redacted]

7.3.1. Diastolic blood pressures (DBP)

Analyses will follow the methods described for the primary and secondary endpoints.

[4]O'Brien E, et al. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. J Hypertens 2013; 31:1731-1768.

[5]Kario K, et al. Guidance on ambulatory blood pressure monitoring: A statement from the HOPE Asia Network. J Clin Hypertens (Greenwich) 2021 Mar; 23(3):411-421.

7.3.2. Nocturnal SBP dipping

Nocturnal SBP dipping magnitude is defined using the 24-hour ABPM data as the difference between average daytime SBP and average nighttime SBP expressed as a percentage of the daytime value.

$$Nocturnal\ Dipping\ Magnitude\ (\%) = \frac{Daytime\ mean\ SBP - Nighttime\ mean\ SBP}{Daytime\ mean\ SBP} \times 100$$

Generally accepted normal values of nocturnal dipping are between 10% and 20%[6]. Nocturnal dipping magnitude will be classified as absent (<10%), normal (≥10% to ≤20%) or extreme (>20%).

Nocturnal dipping magnitudes at each visit, including change from baseline, will be summarized as continuous variables. Nocturnal dipping magnitude classifications at each visit will also be summarized as categorical variables. Crosstabulations and the McNemar-Bowker test will be performed to describe change in nocturnal dipping classification between time points.

7.3.3. 24-Hour Urine Sodium Excretion

24-hour urine sodium excretion at each visit, including change from baseline, will be summarized as continuous variables.

At baseline and EOT, correlation between 24-hour average SBP and 24-hour urine sodium excretion at each visit will be assessed visually by scatterplots and analytically by Pearson and Spearman coefficients.

At EOT, correlation between 24-hour average SBP change from baseline and 24-hour urine sodium excretion change from baseline will be assessed visually by scatterplots and analytically by Pearson and Spearman coefficients.

7.3.4. Participant Global Impression of Change (PGI-C)

Likert scale PGI-C responses will be aggregated as Improved (3 levels), No Change (1 level), or Worsened (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.

7.3.5. Participant Global Impression of Severity (PGI-S)

Likert scale PGI-S responses will be aggregated as Improved (3 levels), No Change (1 level), or Worsened (3 levels).

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.

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[6] Bloomfield and Park, "Night time blood pressure dip". World J Cardiol 2015; 7:373-376.

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

8. SAFETY

Unless otherwise specified, safety analyses are based on the Safety Set.

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.

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).

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

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. 24-Hour Total Sleep Time

Electronic sleep diaries will be completed by the participant daily for approximately 7 days around the time of (and including) each 24-hour BP recording.

For each participant, weekly mean sleep time, weekly mean wake time, and daily and weekly total sleep time (TST) will be calculated.

Weekly mean sleep time and weekly mean wake time will be calculated as the mean of values reported in the participant sleep diary around and including each 24-hour BP recording. Times should be converted to 24-hour format (adding 24 to times denoted as AM; e.g., 1:20 AM = 25:20) and expressed in minutes (multiply hours by 60 and add minutes) to facilitate the calculation before calculating the means. After calculating the mean, convert the result back to a time by dividing the result by 60 and assigning the whole number to hours and the remainder multiplied by 60 to minutes (rounding to nearest whole number). If the number of hours is less than 24, express as PM; if the number of hours is greater than 24, subtract 24 and express as AM.

Daily TST is calculated as ((A – B) – (C + D)), where A is "Awake Time", B is "Sleep Time", C is "Minutes to Fall Asleep", and D is "Minutes Spend Awake" from the electronic diaries. Values

for Sleep Time and Awake Time may be converted to minutes as above to facilitate the calculation; Fall Asleep (C) and Spend Awake time (D) may then be subtracted and the TST result remains expressed in minutes.

Weekly mean TST will be calculated as the mean of daily TST values associated with each visit.

Weekly mean TST at each visit and change from baseline will be summarized as continuous variables. Daily and weekly mean sleep and wake times will be listed, with footnote denoting which values were used for calculating daytime/nighttime windows (see Section 7.2.2).

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

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

- 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, subject 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

8.3. Laboratory Assessments

Results from clinical laboratory assessments described in the protocol will be summarized as continuous variables. Where included in laboratory reports, abnormally high/low or other clinically significant observations will be denoted in listings.

8.4. Pregnancy

Pregnancy results will be presented in listings only.

8.5. Vital Signs

Sitting heart rate, weight, and height at each visit, including change from baseline, will be summarized as continuous variables.

8.6. 12-Lead Electrocardiogram (ECG)

Machine-read ECG parameters at each visit and change from baseline will be summarized as continuous variables.

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

C-SSRS responses and aggregated responses for suicidal ideation or suicidal behavior at screening will be summarized as categorical variables using the Safety Set.

9. PHARMACOKINETIC ANALYSES

Not applicable.

10. PHARMACODYNAMIC ANALYSES

Not applicable.

11. MODIFICATION HISTORY

Version	Date	Description
3.0	05 Dec 2024	• Revisions to align with latest Protocol Amendments. • Updated GMA signatory • Corrected calculation of sleep diary NTST parameter • Corrected reference for AE severity coding • Removed comparison of PGI-S vs PGI-C • Clarified presentation of Protocol Deviations • Clarified O'Brien-Fleming and Pocock alpha levels as one-sided • Clarified application of visit windows in table presentations • Removed presentation of LS mean differences for subgroups
2.1	15 Feb 2024	• Correction to modification history section.
2.0	13 Feb 2024	• General updates to align with Protocol Amendment 2. • Clerical and style updates. • Revised fixed day/night windows to align with international guidance and added threshold for using fixed windows in analysis. • Clarified IA procedure and provided GSD alpha levels.
1.0	05 Jul 2023	Initial version

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse event
AEOSI	Adverse event of special interest
AHA	American Heart Association
ALT	Alanine transaminase
ABPM	Ambulatory blood pressure monitoring
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CP	Conditional power
CRF	Case report form
C-SSRS	Columbia – Suicide Severity Rating Scale
CTMS	Type of deviation and severity
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early discontinuation
EDS	Excessive daytime sleepiness
EOT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat Set
NT1	Type 1 narcolepsy
NT2	Type 2 narcolepsy

OR	Odds ratio
ORE	Other reportable experience
PGIc	Patient global impression of change
PGIs	Patient global impression of severity
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SFU	Safety follow-up
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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.

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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