STATISTICAL ANALYSIS PLAN

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JZP258-401-00

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STUDY TITLE:

A Phase 4 Multicenter, Open-label, Single-arm Study of Safety, Tolerability, Effectiveness and Treatment Optimization in Participants Switching From Xyrem to XYWAV for the Treatment of Narcolepsy

SPONSOR:

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Confidentiality Statement

This study is being conducted in compliance with Good Clinical Practice (GCP) guidelines.

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
bpm	beats per minutes
BUN	blood urea nitrogen
Ca	Calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl	Chloride
CRF	case report form
COVID-19	coronavirus disease 2019
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTMS	clinical trial management system
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
E/D	early discontinuation
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime sleepiness
EOSMS	Ease of Switching Medications Scale
ESS	Epworth Sleepiness Scale
ET	end of treatment
EU	European Union
FDA	Food and Drug Administration
FPQ	Forced Preference Questionnaire

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IRT	interactive response technology
K	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
Na	Sodium
NCI	National Cancer Institute
NT1	Narcolepsy Type 1
NVAS	Nausea Visual Analog Scale
PE	physical examination
PGIc	Participant Global Impression of Change
PHQ-9	Participant Health Questionnaire-9
PK	Pharmacokinetic
PR	pulse rate
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
US	United States
WBC	white blood cell count
WHO	World Health Organization

2. MODIFICATION HISTORY

Version History for SAP:

Version	Date	Description
V1.0	*09 NOV 2022*	Original SAP
V1.1	*12 DEC 2022*	Removed references to ATC coding, updated MedDRA and WHODRUG database versions.

3. 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 JZP 258-401-00, "A Phase 4 Multicenter, Open-label, Single-arm Study of Safety, Tolerability, Effectiveness and Treatment Optimization in Participants Switching from Xyrem to XYWAV for the Treatment of Narcolepsy" for inclusion in the Clinical Study Report (CSR). The current version is based on Original Protocol dated 08Dec2020. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the interim and/or final CSR.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Objective

The objective of this study is to describe the clinical experience of participants switching from Xyrem to XYWAV for the treatment of narcolepsy with or without cataplexy in terms of safety, tolerability, effectiveness, and treatment optimization.

4.1.2. Exploratory Objective

The exploratory objective of this study is to describe the ease of conversion and participant preference of XYWAV in participants with narcolepsy with or without cataplexy.

4.2. Study Endpoints

4.2.1. Key Endpoints

- Adverse Events and Serious Adverse Events
- Change in the Nausea Visual Analog Scale
- Change in weekly rate of cataplexy attacks (for Narcolepsy Type 1)
- Change in Epworth Sleepiness Scale to assess excessive daytime sleepiness
- Participant Global Impression of Change
- Time to optimized dose and regimen
- Number of changes from first dose and regimen to optimized dose and regimen
- Number of participants dosing fasted versus dosing without consideration of food
- Timing and characterization of meals relative to dosing

4.2.2. Exploratory Endpoints

- Ease of Switching Medications Scale
- Forced Preference Questionnaire

5. STUDY DESIGN

5.1. Summary of Study Design

Study JZP258-401 is an open-label, single-arm, interventional study that is intended to provide descriptive assessments of safety, tolerability, effectiveness and optimization of treatment during participant transition from Xyrem to XYWAV. The dosing information obtained in this trial may be used to support that XYWAV can be dosed with or without food. If warranted, the data obtained from this study would be included to support future label discussions with regulatory agencies.

The target study population is participants with narcolepsy, with or without cataplexy that have remained on a stable regimen of Xyrem for no less than 2 months prior to start of this study, at any prescribed dose (up to a maximum of 9 grams) taken once, twice, or thrice nightly and with no single dose exceeding 6 grams.

5.2. Study Treatment

All participants will continue to stay on stable Xyrem dose and regimen during screening and baseline periods. During the Open Label Conversion and Treatment Optimization period, participants will switch to XYWAV initially at the same dose (gram-per-gram) and regimen as Xyrem, then expand the dose and regimen upon optimization with or without food. The total duration of the study is expected to be approximately 17 months, with duration of individual participant participation around 3 to 3.5 months. The study (Figure 1) comprises the following phases:

Screening Period (Up to 30 days)

To be eligible for the study, all participants must have been titrated to a tolerable and effective dose and regimen of Xyrem (with or without concomitant anticataplectics or stimulants), which shall have remained stable for ≥ 2 months prior to entry into study. During the initial Screening period of up to 30 days, all participants will be evaluated for eligibility based on screening assessments, with the option to be rescreened once if the rescreening is approved by the Medical Monitor. Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (eg, unstable hypothyroidism) and is permitted only with the permission of the Medical Monitor. Participants who are approved for rescreening must be re-consented if re-screening occurs more than 28 days after the first consent, in which case, a new participant identification number should be assigned, and all screening procedures should be repeated.

Baseline Period (2 weeks)

Following study entry, participants will remain on the same stable dose and regimen of Xyrem during a 2-week Baseline period. Baseline weekly rates of cataplectic attacks and ESS scores (as a measure of EDS) will be determined in this period, in addition to other baseline treatment and safety measures as outlined in Schedule of Activities (Protocol JZP258-401-00 Section 1.3).

Intervention (Open-Label Conversion and Treatment Optimization) Period (6 weeks)

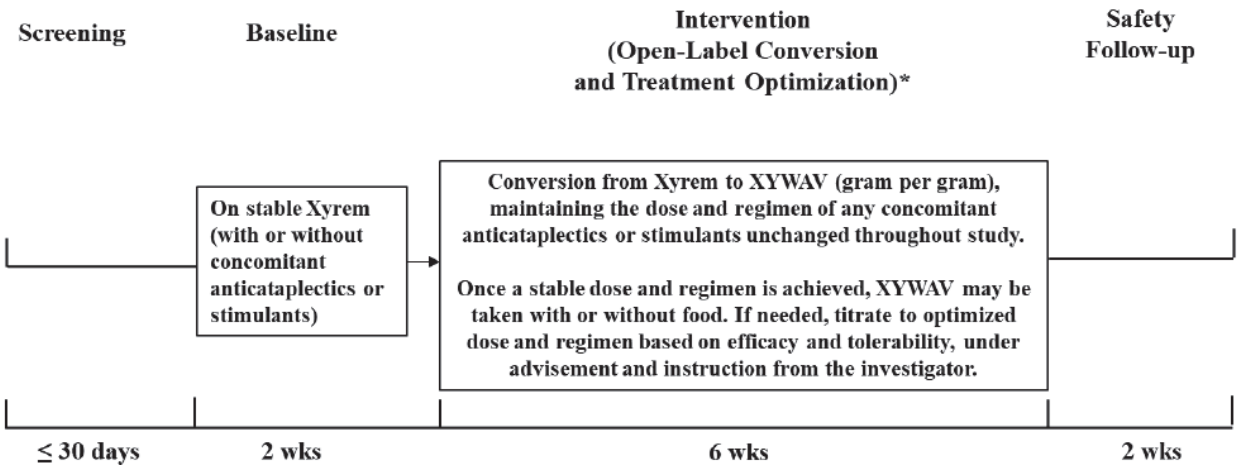
During the Intervention (Open-Label Conversion and Treatment Optimization) period, participants on a stable dose and regimen of Xyrem will be switched to the same dose (gram-per-gram) and regimen of the study intervention drug (XYWAV). Any concomitant anticataplectics or stimulants will be maintained as per their current dose and regimen throughout the study.

Once the investigator determines that a stable dose and regimen has been achieved, XYWAV may be taken with or without food. If needed, XYWAV may be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator, with the goal to end the period with ≥ 2 weeks of optimized therapy on XYWAV.

Safety Follow-up Period

Following the Intervention period, participants will return for a Safety Follow-up visit 2 weeks after the End of Treatment (ET) or Early Discontinuation (E/D). Following the ET or E/D, including during the Safety Follow-up period, it is understood and expected that investigators will determine the appropriate course of care with the participant, and may resume any prescribed medications that were discontinued prior or during the study. There is no plan to monitor participants beyond the 2-week Safety Follow-up period.

Figure 1 Overall Design of Study JZP258-401



*Adjustment to achieve optimal clinical benefit, with adequate control of cataplexy and EDS while maintaining tolerability per investigator judgment.

Abbreviation: EDS = excessive daytime sleepiness; wks = weeks

5.3. Power and Sample Size Considerations

An estimated total of 100 participants will be enrolled into this single-arm study. This number is considered sufficient to meet the study objectives. A formal sample size calculation has not been performed and formal hypothesis testing is not planned for data in this study.

5.4. Randomization and Blinding

All participants who sign the informed consent form (ICF) will receive a participant number. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant. Study JZP258-401 is an open-label, single-arm trial, and therefore will have no blinding. Treatment allocation for this study will occur centrally through the use of an interactive response technology (IRT).

5.5. Interim Analysis

Based on enrollment, an optional interim analysis may be conducted after approximately the first 25 participants and 50 participants respectively, have completed or prematurely terminated the study to provide an early understanding of the clinical experience of participants switching from Xyrem to XYWAV. This data may be presented externally. This process will occur with no pause in enrollment.

As formal hypothesis testing is not performed, no alpha adjustments will be made for any interim analyses.

A Data Monitoring Committee will not be used for this study.

6. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Table 1 Analysis Set

Analysis Set	Description
All Screened	The All Screened Analysis Set will include all subjects who provided a signed informed consent for this study. This analysis set will be used to summarize the number of screened, screen failure and enrolled subjects.
Enrolled	All participants who sign the informed consent form and meeting all eligibility criteria for the study. This analysis set will be used to summarize participant disposition, major protocol deviations (as classified in CTMS), and inclusion/exclusion from the Safety Analysis Set, including reasons for exclusion from it.
Safety	The Safety Analysis Set will include all participants in the Enrolled Analysis set who take at least one dose of Xyrem after providing informed consent. This analysis set will be used for summaries of all endpoints, except those which only pertain to data captured during the Intervention Period.

Analysis Set	Description
XYWAV Safety	The XYWAV Safety Analysis Set will include all participants in the Safety Analysis Set who take at least one dose of XYWAV. This analysis set will be used for summaries of all endpoints which pertain to only data captured during the Intervention Period.
XYWAV Efficacy	The XYWAV Efficacy Analysis Set will include all participants in the XYWAV Safety Analysis Set who finish the course of study. This analysis set will be used for summaries of all endpoints which pertain to only data captured during the Intervention Period.

7. 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).

7.1. General Methods

Assessments of all study endpoints (as listed in Section 4.2 will be summarized descriptively. Formal hypothesis testing will not be performed.

In general, categorical variables will be reported as frequency and percent. Continuous variables will be reported as the number of participants, mean, standard deviation (SD), or standard error (SE), median, minimum and maximum or range.

For quantitative measures, change from baseline will be calculated as:
Change from baseline = test value at Visit X – test value at baseline

All data will be summarized in tables with a single “overall” column for statistics. As applicable, data will be summarized by visit and/or study period.

All summaries, statistical analyses, and individual participant data listings described below will be completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

7.2. Baseline and Study Day Definitions

7.2.1. Baseline

For all safety assessments and effectiveness summaries across the study, study baseline will be defined as the last non-missing measurement collected/ assessed during the Baseline (Xyrem) Period in which participants remain on a stable Xyrem dose and regimen, with or without concomitant anticataplectics or stimulants. First dose of XYWAV will be administered in the first night of Visit 3. Assessment and data collected in the baseline period up till that night, will be included in this period.

7.2.2. Study Day

The screening period is from Day -30 to Day -1. The 2-week baseline period is Day 1 to Day 14. Participants on a stable dose and regimen of Xyrem will be switched to XYWAV treatment at the beginning of the Intervention (Open-label Conversion and Treatment Optimization) period, starting the night of Visit 3/Day 15 and continue through to the End of Treatment (ET) (Visit 8) or Early Discontinuation (E/D) visit, as applicable.

Study day will be calculated as:

Study Day = (the date of assessment or event - the first day of the baseline period (Visit 2)) + 1

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

7.2.3. Visit Windows

Except where specified, all data will be summarized using the CRF visit at which the data was collected. Where data is captured at an Early Termination visit, those data will be summarized with the regular visit at which the assessment would have been captured, relative to the study period during which the participant withdrew. For example:

- If a participant early discontinues during the Baseline Period, i.e. prior to the first dose of XYWAV, then data should be mapped to Visit 3.
- If a participant early discontinues during the Intervention Period, i.e. after at least one dose of XYWAV, then data should be mapped to the next scheduled visit at which those data would have been captured, based on the Schedule of Assessments.

For data captured independent of a CRF visit, eg, Adverse Events, Concomitant Medications and Cataplexy Diary, the following rules will apply:

- If the reported date is on or prior to first dose of XYWAV then the data will be considered to be included into the Xyrem Baseline Period for summaries
- If the reported date is after the first dose of XYWAV while on or prior to the completion of treatment or early discontinuation, then the data will be considered to be included into the XYWAV Intervention Period for summaries.

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. In addition, unscheduled visits with the assessment date earlier than the date of first dose of XYWAV, or participants early discontinue the study prior to the first dose of XYWAV, the data can only be mapped up to Visit 3. If the assessment date is later than the date of first dose of XYWAV, the unscheduled data should not be mapped to any visit prior to Visit 3.

Study Period	Study Visit	Target Study Day
Baseline	Visit 2	1
Intervention	Visit 3	15

Intervention	Visit 4	22
Intervention	Visit 5	29
Intervention	Visit 6	36
Intervention	Visit 7	43
Intervention	Visit 8	57

Where summaries require a period of time, eg, the last week of a study period, this will be determined based on the actual visit date, as long as the above rule is maintained. For example, if a participant has a first dose of XYWAV on Day 15 and Early Terminates on Day 20, the last week of XYWAV will be only Days 16-20, as the participant received Xyrem on Days 14 and 15 (the first dose of XYWAV being taken the night of Day 15). Imputation due to the missing data this approach generates will follow rules outlined in Section 7.2.4.

7.2.4. 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. Any missing data for diary data for cataplexy attacks and Nausea Visual Analog Scale (NVAS), or any missing item score for Epworth Sleepiness Scale (ESS) will be treated as follows:

- For participants experiencing at least 1 day of non-missing cataplexy attack, the weekly number of cataplexy attacks will be derived as the average number of daily attacks from days with non-missing data within the week, multiplied by 7. Note: 1 or more daily entries in the cataplexy attack dairy are required to be completed for the weekly average cataplexy attack calculation. Otherwise, the weekly score is recorded as missing.
- For participants with at least 1 day of NVAS data, the NVAS for that week will be the average daily score from days with non-missing data within the week, then multiplied by 7.
- For participants experiencing 3 or more ESS item scores missing at a specific timepoint, the ESS total score will be set to missing. If 1 or 2 ESS item scores are missing at a specific timepoint, the mean of remaining 7 or 6 non-missing ESS item scores at that timepoint will be used to impute the missing ESS item value. ESS total score will be calculated as the sum of the observed and imputed item scores.

7.3. Hypotheses Testing

All endpoints (listed in Section 4.2) will be summarized descriptively. Formal hypothesis testing will not be performed.

7.4. Level of Significance & Multiplicity Adjustment

As this study does not test a formal hypothesis, there is no multiplicity adjustment. For specific statistics, for example, difference in proportions, 95% CI based on normal approximation will be generated.

7.5. Subgroups and Subgroup Analyses

Subgroup analyses will be performed when applicable. See Section 9.1.7.

7.6. Changes to Planned Analyses

The changes in planned analyses between the protocol and SAP are the following:

- All Screened Analysis Set, XYWAV Safety Analysis Set and XYWAV Efficacy Analysis set are added in addition to the analysis sets defined in protocol section 9.3. Exclude potential screen failures from Enrolled Analysis Set defined in protocol section 9.3.
- National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0 or higher is added as the reference for AE severity classification.

8. STUDY POPULATION SUMMARIES

8.1. Enrollment

The total number and percentage of participants for each Analysis Set defined in Section 6 will be summarized. The number of participants who enrolled by country and study site/Investigator will be summarized.

8.2. Subject Disposition

All participants who provide informed consent will be accounted for 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, including reasons for discontinuation, will be presented using the enrolled analysis set.

Note that coronavirus disease 2019 (COVID-19) impacts throughout the study will be captured at each non-remote visit for the type of visit performed due to COVID-19 and study related impacts due to COVID-19. These will be summarized by visit based on enrolled analysis set.

8.3. Demographic and Baseline Characteristics

Demographic and other baseline characteristics data will be summarized using descriptive statistics for the safety analysis set.

Demographic and other baseline characteristics include:

- 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. (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).
- Gender
- Race - participants who reported more than one race will be reported under ‘multiple’ race category

- Ethnicity
- Childbearing potential
- Baseline weekly cataplexy attack rate
- Baseline ESS score

8.4. Medical/Surgical History

Surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 24.0, and are defined as those medical conditions/ diseases which started prior to or on the date of initial ICF signing.

Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT) for the safety analysis set. If a participant reports a past medical condition/disease, surgery or past medication more than once within a SOC or PT, the medical condition/disease, surgery or past medication will be reported only once for that SOC or PT.

8.5. Prior and Concomitant Medications

Medications will be coded to the preferred drug name using the World Health Organization (WHO) drug dictionary, version GLOBALB3Mar21, and will be classified as follows:

- **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 summarized by preferred drug name based on the safety analysis set. A listing will also be presented.

8.6. Protocol Deviations

Protocol deviations as classified in the CTMS (type of deviation and severity) will be summarized across all study periods using enrolled analysis set.

Changes to study conduct due to COVID-19 restrictions will be reported as protocol deviations and summarized. All protocol deviations will also be provided in a listing.

These COVID-19 related deviations will be summarized separately by the classification type in CTMS and included in a listing.

9. EFFECTIVENESS

9.1. Key Effectiveness Endpoints and Analysis

Unless otherwise specified, effectiveness data will be primary summarized using both the XYWAV Safety Analysis Set and XYWAV Efficacy Analysis Set.

9.1.1. Rate of Cataplexy Attacks

Narcolepsy Type 1 (NT1) participants will be required to complete an electronic Cataplexy Frequency Diary daily. 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 7. The baseline value for cataplexy attack is the weekly rate of the last week of the baseline period on Xyrem. For example, if the first dose of XYWAV is taken in the night of Day 16, the last week of baseline would be approximately Day 10 to Day 16, prior to the time of first dose of XYWAV. After conversion, the weekly rate for each visit will be based on the days within the visit window as in Section 7.2.3.

Weekly rate for baseline and each visit will be summarized with number of participants, mean, SD, median, min and max. Changes in weekly cataplexy rate from the study baseline to that of each visit during the intervention period will be summarized with number of participants, mean, standard deviation, median, minimum, and maximum. Changes in weekly cataplexy rate from the XYWAV baseline to that of each visit after XYWAV conversion during the intervention period will be also summarized in a similar manner. Box-whisker plot weekly rate of cataplexy attack will be plotted over time.

Cataplexy attack rate will only be determined for NT1. If NT2 participants provide cataplexy attack diary data, those data will be listed but excluded from the summary of the endpoint.

9.1.2. Epworth Sleepiness Scale (ESS)

The ESS measures EDS in 8 different situations with four choices of responses from 0 to 3. ESS total score ranges from 0 to 24.

The ESS questionnaire will be completed by the participants at the baseline visit and at the End of Treatment (ET) visit.

ESS scores will be summarized for the baseline, ET, and the mean change from baseline at ET for all participants. Summarized statistics will include number of participants, mean, standard deviation, median, minimum, and maximum. Mean (± SD) ESS scores will be plotted over time.

A listing of all ESS data will be presented.

9.1.3. Participant Global Impression of Change (PGIc)

PGIc measures participant's impression of improvement in the sleepiness from previous visit. There are 7 categories ranging from very much improved to very much worse with 3 categories for improvement, 3 categories for no improvement, and one category for no change.

PGIc data will be collected at the end of the treatment period or at Early Discontinuation. A summary statistics report will include the number of participants, tabulation of each of the 7 categories and percent. The number and percent of participants reported improved and worsen will be generated.

9.1.4. Dose and Regimen Changes in Intervention Period

Time to optimize dose and regimen is defined as the time (unit is day) from the first dose and regimen of XYWAV to the optimized dose and regimen of XYWAV, where the optimized dose and regimen is the final dose and regimen that remains unchanged throughout the remainder of the intervention period. Optimized dose and regimen is defined as follows:

- The final dose and regimen that a participant takes before or at Visit 7 that remains unchanged to Visit 8 when the participant completes the XYWAV treatment, regardless of the time between Visits 7 and 8.
- The final dose and regimen that remains the same for at least 2 weeks (14 days) for a participant who completes at least 21 days post conversion and then terminates the XYWAV treatment early. For example, a participant changes dose and/or regimen after 1 week (7 days) post conversion and terminates from the study at Day 38, but remains on stable dose and regimen from Day 24 to Day 37.

Summary of dose and regimen changes will be based on XYWAV Safety analysis set per below:

The time to achieve optimized dose and regimen will be summarized with number of participants, mean, SD, median, minimum, maximum.

The number of changes in dose and regimen from first XYWAV dose to achieve optimized dose and regimen will be summarized with mean, SD, median, minimum, maximum.

9.1.5. Characterization of Meals Relative to Dosing

Once a participant has reached optimized dose and regimen, the investigator may decide to instruct the participant to dose without regard to food. The number of participants and percentage in each group (fasted versus without consideration of food), tabulation of the food types (regular meal, snack, drink) and percentage will be summarized.

9.1.6. Sensitivity Analyses

Not applicable

9.1.7. Subgroup Analyses

Unless specified, all endpoints will be summarized separately for participants identified as NT1 and NT2. Cataplexy attacks, ESS and PGIc will be summarized separately for those who achieved optimized dose and those that did not achieve optimized dose. Summary tables of statistics will be produced as described in Sections 9.1.1 through 9.1.3.

9.2. Exploratory Endpoints

9.2.1. Ease of Switching Medication Scale (EOSMS)

The EOSMS questionnaire will be administered in electronic format to participants at the ET or E/D visits where a participant will evaluate the process of switching from Xyrem to XYWAV with one of 5 choices (extremely easy, easy, neither easy nor difficult, difficult, extremely difficult). These answers will be tabulated with number and percent for each category of answer based on XYWAV Safety analysis set. A listing of EOSMS will be presented.

9.2.2. Forced Preference Questionnaire (FPQ)

FPQ questionnaire are given to participants at the ET or E/D visit where they will give their preference of treating their narcolepsy with Xyrem or XYWAV. The preferences will be tabulated with number and frequency based on XYWAV Safety analysis set. A listing of FPQ will be presented.

10. SAFETY AND TOLERABILITY

Unless otherwise specified, safety analyses will be based on the safety analysis set. Only summary statistics will be provided.

10.1. Exposure

10.1.1. Extent of Exposure

Exposure to Xyrem is during in baseline period and exposure to study drug XYWAV is in the Open Label Conversion and Treatment Optimization Period (intervention period) (see Section 5.2). Summary statistics, for the exposure duration (days) for Xyrem during the baseline period and XYWAV during the intervention period, number of participants, mean, standard deviation, median, and range will be tabulated.

A listing will be produced for both Xyrem and XYWAV exposure details.

10.1.2. Treatment Compliance

Compliance will be calculated for XYWAV Safety analysis set only.

XYWAV is taken as oral solution at a total salt concentration of 0.5g per mL, Table 2 shows the corresponding volume to the assigned dose level. XYWAV compliance will be calculated as the

volume of solution taken during a study period (ie, total dispensed – total returned) divided by the volume of solution that should have been taken by the participant during that intervention period, 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 denominator is the sum of daily volume that should be taken according to the prescribed dose and regimen for the day.

Compliance will also be summarized by category (<75%, 75-125% and >125%) for the intervention period. A listing of compliance will also be presented.

Deviations from the prescribed treatment regimen or dosage including overdosing at greater than the maximum allowable daily dose of 9 grams or any single dose exceeding 6 grams will be summarized.

Table 2 Total Daily Volume of Solution (mL)

Assigned or Stable Dose of Study Drug (g)	Volume of Solution (mL)
4.5	9
5.0	10
5.5	11
6.0	12
6.5	13
7.0	14
8.0	16
9.0	18

10.2. Adverse Events

Adverse events (AEs) occurring from the initial participant ICF signature date until the end of Safety Follow-up visit will be reported. If the Investigator becomes aware of a serious adverse event (SAE) within 30 days after the last dose of study drug XYWAV, the event must also be reported. In addition, any SAE assessed as related to study drug or procedure by the Investigator must be reported regardless of time elapsed after study termination.

Adverse events recorded in the case report form will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0. 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.

Note that participants who acquire COVID-19 or report AEs due to the COVID-19 public health emergency (eg anxiety) while on study will be coded accordingly and included in the adverse event summaries.

AEs are defined in this study as follows (Protocol Appendix 7):

- A 'Xyrem-emergent AE' refers to an AE that began or worsened in the period following signing of the informed consent and before administration of the first study intervention (XYWAV) dose (i.e., including the Screening period through the Baseline [Xyrem-stable dose and regimen] period till the first dose of XYWAV)
- A treatment-emergent adverse event (TEAE) refers to an AE that either began or worsened after administration of the first dose of study intervention drug (XYWAV) to End of Treatment (ET) period (prior to the Safety Follow-up period).
- Safety follow-up AEs are defined as occurring after the last dose date until 30 days after the last dose date
- Unless specified, the term AEs will include both Xyrem-emergent AEs, TEAEs and Safety follow-up AEs.
- Safety follow-up AEs will not be considered as either Xyrem-emergent AEs or TEAE. They will not be included into summary tables but will be presented in listings.
- Xyrem-emergent AE related summaries will be based on safety analysis set.
- TEAE related summaries will be based on XYWAV Safety analysis set.

An overall summary on Xyrem-emergent AE and TEAE with following categories will be provided:

- Subjects with any Xyrem-emergent AE/TEAE
- Subjects with any drug-related Xyrem-emergent AE/TEAE
- Subjects with any serious Xyrem-emergent AE/TEAE
- Subjects with any Xyrem-emergent AE/TEAE by severity
- Subjects with any Xyrem-emergent AE/TEAE with outcome as death
- Subjects with any Xyrem-emergent AE/TEAE leading to drug withdrawal
- Subjects with any Xyrem-emergent AE/TEAE leading to drug dose reduction
- Subjects with any Xyrem-emergent AE/TEAE leading to drug dose increase
- Subjects with any Xyrem-emergent AE/TEAE leading to drug interruption

In addition, subject incidence of Xyrem-emergent AEs/TEAEs will be summarized by following:

- SOC and PT
- PT only
- Maximum Severity by SOC and PT
- Drug-related by SOC and PT
- Xyrem-emergent AE/TEAE leading to drug withdrawal by SOC and PT

For data listings, all following will be presented:

- All AEs
- AEs with an outcome of death
- AEs leading to drug withdrawal
- Serious AEs

If a participant has multiple events with the same PT occurring in different periods, the event will be reported for each of those periods. Participant 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. For summaries by PT only, PTs will be sorted in descending order of overall frequency.

10.3. Physical Examinations

A complete PE will be done in the screening period where at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems; breast and genitourinary exams are excluded. Any abnormality identified at the screening PE will be recorded as medical history.

10.4. Clinical Laboratory Assessment

Clinical laboratory assessments are listed in Table 3 below. Certain clinical laboratory assessments (eg, comprehensive metabolic panel, hematology, urinalysis and serum pregnancy testing) will be performed for screening purposes only, whereas other clinical laboratory assessments (eg, urine drug, and alcohol screening) will be performed at various study time points.

Hematology, serum chemistry and urinalysis at screening will be summarized and listed. In data listings, any out of reference range values will be flagged as high/low, further clinically significant lab results will be flagged in listings if applicable.

Abnormal laboratory assessments deemed clinically significant by the investigator will be reported as an adverse event.

All other laboratory results, including pregnancy test, drug screen, and alcohol screen, will also be presented in data listings.

Table 3 List of Laboratory Tests

Hematology:	**Serum Chemistry:**
- Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential	- Albumin (ALB) - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT)

<table>
<tr>
<td>Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen</td>
<td rowspan="4">- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Magnesium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid
- Thyroid stimulating hormone (TSH)(screening only)</td>
</tr>
<tr>
<td>*Serum Pregnancy Screen</td>
</tr>
<tr>
<td>Drug Screen (urine)</td>
</tr>
<tr>
<td>Alcohol Screen</td>
</tr>
<tr>
<td colspan="2">*Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as >1 year of amenorrhea), who have medically documented ovarian failure (defined as serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.</td>
</tr>
</table>

10.5. Pregnancy Testing

Pregnancy testing is required for all females of childbearing potential in the screening period unless otherwise exempt (see Table 3). Additional pregnancy tests may be performed, as deemed necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study. A listing of pregnancy results will be presented.

10.6. Vital Signs

The following vital signs measurements will be reported for this study.

- Sitting systolic blood pressure (SBP), (millimeter of mercury [mmHg])
- Sitting diastolic blood pressure (DBP) (mmHg)
- Sitting heart rate (beats per minute [bpm])
- Sitting respiratory rate (breaths/minute)

- Body Temperature (°C)

These vital signs will be measured during the screening visit and each in-clinic scheduled visit, according to the schedule of activities.

The observed and change from baseline vital signs across all study periods will be summarized by visit. Change from XYWAV Conversion Day will also be summarized for visits after conversion. In addition, number and percentages of subjects with at least one abnormal vital signs (based on criteria at Table 4 below) will be summarized by visit.

A listing of vital signs with flagged abnormal values will also be presented.

Table 4 Vital Signs Predefined Markedly Abnormal Criteria

Parameter (unit)	Low	High
SBP (mmHg)	< 90 mmHg	> 140 mmHg; > 160 mmHg
DBP (mmHg)	< 50 mmHg	> 90 mmHg; > 100 mmHg
Heart rate (bpm)	< 60 bpm	> 100 bpm
Respiratory Rate	< 12 breaths/min	> 20 breaths/min
Temperature (°C)	< 36.0 °C	> 38.0 °C

10.7. Electrocardiograms

Electrocardiograms will be reported during the Screening visit with the following ECG parameters:

- Overall ECG assessment:
  - Normal
  - Abnormal, not clinically significant
  - Abnormal, clinically significant

A table of summary statistics will contain count and frequency for the discrete variables (normal, abnormal/not clinical significant, abnormal/clinical significant) and count. An ECG listing will also be presented.

10.8. Nausea Visual Analog Scale

Tolerability associated with Xyrem and XYWAV will be measured based on an NVAS assessment.

For NVAS, the baseline value is defined as NVAS evaluation performed daily over the last 7 days of the Xyrem-stable Baseline Period. For missing NVAS assessment handling, please see Section 7.2.4. The NVAS results for the baseline, end of treatment, and the change from the baseline period will be summarized with number and frequency of having nausea or not, and the mean (SD), median, and range. 95% CI of the mean change in NVAS from the baseline will be estimated. A listing will also be presented.

10.9. Suicidal Ideation and Behavior Risk Monitoring

XYWAV and Xyrem are considered CNS depressants. Columbia-Suicidal Severity Rating Scale (C-SSRS) will be administered to participants during the screening period to exclude any individuals with active suicidal ideation or behavior. A listing of C-SSRS scores will be presented.

10.10. Participant Health Questionnaire-9

The Participant Health Questionnaire-9 (PHQ-9) scale is a depression assessment that scores each of the 9 DSM-IV criteria for major depressive disorder with 4 scores (0 = not at all, 1 = several days, 2 = more than half of the days, 3 = nearly every day). Total scores are summed up to 27 across all 9 criteria with higher score suggesting a more depressed condition. For score interpretation, total PHQ-9 scores can be divided into 5 depression severity grades: 1-4 (minimal depression), 5-9 (mild depression), 10-14 (moderate depression), 15-19 (moderately severe depression) and 20-27 (severe depression).

A table with summary statistics for total scores and overall score interpretation categories will be presented. A listing will also be presented.

11. PHARMACOKINETIC ANALYSES

Not applicable.

12. PHARMACODYNAMIC ANALYSES

Not applicable.

APPENDICIES

Appendix 1.1: 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 Start Date

If *year* is missing (or completely missing):

- If AE end date is also missing or AE end date ≥ first XYWAV dose date: set to the first XYWAV dose date.
- If AE end date < the first XYWAV dose date: set to the informed consent date.

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

- If *year* = year of the first XYWAV dose: set the date to the first XYWAV dose date.
- If *year* < year of the first XYWAV dose: set *month* and *day* to December 31st, compare with inform consent date, take the later one.
- If *year* > year of the first XYWAV dose: set *month* and *day* to January 1st, compare with last known study date (including follow up period), take the earlier one.

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

- If *year* = year of first XYWAV dose, and:
  - If *month* = month of first XYWAV dose: set *day* to day of first XYWAV dose.
  - If *month* < month of first XYWAV dose: set *day* to last day of *month*, compare with inform consent date, take the later one.
  - If *month* > month of first XYWAV dose: set *day* to 1st day of *month*, compare with last known study date (including follow up period), take the earlier one.

- If *year* < year of first XYWAV dose: set *day* to last day of month, compare with inform consent date, take the later one.
- If *year* > year of first XYWAV dose: set the drug to XYWAV and set *day* to 1st day of month, compare with last known study date (including follow up period), take the earlier one.

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

Appendix 2.2: Prior/Concomitant Medications Date Imputation Rules

Partially missing start/end dates for prior/concomitant medications will be imputed in the ADaM dataset for prior/concomitant medications/procedures. If the imputed start date is after the end date based on rules below, the start date will be imputed by the end date further.

Incomplete Prior/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 Prior/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.

Appendix 2: Listing of Anticataplectics and Stimulants

Below are the medication names that are considered as anticataplectics, stimulants/alerting agents:

Anticataplectic:
- Xyrem

Anticataplectic /Alerting agent:
- Pitolisant (Wakix)
- Atomoxetine (Strattera)

Anticataplectic:
- Agomelatine
- Amitriptyline
- Atomoxetine (Strattera)
- Bupropion (Wellbutrin)
- Citalopram (Celexa)
- Clomipramine (Anafranil)
- Desipramine
- Duloxetine (Cymbalta)
- Escitalopram (Cipralex, Lexapro)
- Fluoxetine (Prozac)
- Imipramine
- Mirtazapine
- Moclobemid
- Paroxetine (Paxil)
- Protriptyline (Vivactil)
- Reboxetine (Edronax)
- Venlafaxine (Argofan, Effexor, Trevilor)

Stimulant/Alerting agent:
- Amfetamine
- Amfetamine Aspartate
- Amfetamine Sulfate
- Armodafinil
- Atomoxetine
- Dexamfetamine
- Dexamfetamine Saccharate
- Dexamfetamine Sulfate
- Dextroamphetamine - amphetamine salt
- Dexmethylphenidate
- Dexmethylphenidate Hydrochloride
- Lisdexamfetamine Mesilate
- Mazindol
- Methamphetamine
- Methylphenidate
- Methylphenidate Hydrochloride
- Modafinil
- Pitolisant
- Pitolisant Hydrochloride
- Solriamfetol

This list can be updated as the study progresses. All recorded medications will be reviewed by clinical development on an ongoing basis. The final list of anticataplectics and stimulants/alerting agents will be maintained by data management.

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Envelope Id: B2BAC2CB135048F787E8AA46B59DCD87
Status: Completed
Subject: Complete with DocuSign: JZP258_401_SAP_v1.1_clean.pdf
Source Envelope:
Document Pages: 30
Signatures: 5
Envelope Originator:
Certificate Pages: 6
Initials: 0
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AutoNav: Enabled
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[redacted]
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[redacted]
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Record Tracking

Status: Original
12/12/2022 10:24:20 AM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Manager, Biostatistics, Medical Affairs Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 2A1B822B-ED23-4CF4-922D-5AFDFA423A6E Using IP Address: 163.116.140.61 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2022 10:33:12 AM Viewed: 1/3/2023 8:46:57 AM Signed: 1/3/2023 8:48:58 AM
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[redacted] Clinical Scientist, Neuroscience Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Drawn on Device Signature ID: 1CA9611A-D023-4665-90A9-1D8A79A292D0 Using IP Address: 163.116.140.61 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2022 10:33:13 AM Viewed: 12/12/2022 2:25:10 PM Signed: 12/18/2022 12:37:57 PM
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Signer Events	Signature	Timestamp
[redacted] [redacted] Sr Director, Biostatistics Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 70112D85-78B4-4EE9-A211-1E8C1ED85541 Using IP Address: 163.116.144.34 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2022 10:33:12 AM Viewed: 12/15/2022 5:41:49 AM Signed: 12/15/2022 5:42:40 AM
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[redacted] [redacted] Sr. Principal Statistician Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: FE9E8018-58C0-4A8B-B742-49EF5003ECDF Using IP Address: 163.116.248.45 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2022 10:33:11 AM Viewed: 12/12/2022 10:34:17 AM Signed: 12/12/2022 10:36:22 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Sr Dir, Global Medical Affairs Jazz Pharmaceuticals Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 2CC393D2-C395-45CE-9585-E864EADD95EB Using IP Address: 163.116.135.90 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this GxP document	Sent: 12/12/2022 10:33:13 AM Viewed: 12/12/2022 10:35:31 AM Signed: 12/12/2022 10:37:04 AM
Electronic Record and Signature Disclosure: Accepted: 11/1/2021 10:48:43 AM ID: 1d0e2043-44f0-4883-94b2-95893003003b Company Name: Jazz Pharmaceuticals		

In Person Signer Events	Signature	Timestamp

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

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Notary Events	Signature	Timestamp

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Envelope Sent	Hashed/Encrypted	12/12/2022 10:33:13 AM
Certified Delivered	Security Checked	12/12/2022 10:35:31 AM
Signing Complete	Security Checked	12/12/2022 10:37:04 AM
Completed	Security Checked	1/3/2023 8:48:58 AM

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