

TITLE PAGE

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

Study Number: JZP258-407

Protocol and Amendment Number: JZP258-407-03

Amendment Scope: Global

Compound: JZP258 (XYWAV® [low-sodium oxybate oral solution])

Brief Title: An Open-Label Study to Investigate the Effect of XYWAV on Sleepiness, Polysomnography, and Functional Outcomes in Participants With Idiopathic Hypersomnia or Narcolepsy

Study Phase: Phase 3/Phase 4

Acronym: Jazz DUET (Develop hypersomnia Understanding by Evaluating XYWAV Treatment)

Sponsor Name: Jazz Pharmaceuticals, Inc.

Legal Registered Address: 3170 Porter Drive, Palo Alto, California 94304 USA

Regulatory Agency Identifier Number(s): [REDACTED] EU Clinical Trial Number: 2023-508133-13-00

Refer to the final page of this protocol for electronic signature and date of approval.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 03	Please see appended electronic signature page for the date.
Amendment 02	07 Nov 2023
Amendment 01	30 Jun 2023
Original Protocol	31 Mar 2023

Amendment 03

This amendment is considered to be substantial based on the criteria set forth in EU Regulation No 536/2014 of the European Parliament.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to allow for Canadian participants to enroll in the > 9-gram cohort. In addition, the eligibility criteria were updated to state that those who have participated in a different study of XYWAV may enroll directly into this study without waiting 30 days or 5 half-lives (whichever is longer) prior to screening. Finally, sample size assumptions were updated to account for participants in the narcolepsy cohort [REDACTED]

These revisions, along with additional revisions for operational clarity and accuracy, are described in the table below. Minor editorial and formatting changes are not included.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.1 Study Intervention(s)/Treatment(s) Administered 8.3 Safety Assessments	[REDACTED]	This change provides Canadian participants with an additional option for dose optimization and continuity of care, if deemed appropriate by the investigator.
1.1 Synopsis 9.6 Sample Size Determination	Updated sample size assumptions for the narcolepsy cohort.	[REDACTED]
2.1.2.1 Existing Elements of Prescribing Information 8.3 Safety Assessments	Updated reference to USPI location of language stating the prohibition of (contraindicated) combination with alcohol and sedative hypnotics. Added relevant locations to the PM for each statement.	Correction; the relevant USPI section is Section 4. Relevant sections of the PM were added to each statement to reflect the inclusion of Canadian participants in the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added assessments for vital signs and C-SSRS (since last visit) during the Weekly Titration Check-in [REDACTED].	Corrections; assessments were inadvertently omitted from the SoA and were updated to align with text in Section 2.1.2.3 [REDACTED].
	Clarified that vital signs are not recorded if the Weekly Titration Check-in occurs via telecom for participants [REDACTED].	Clarification; vital signs are measured during in-clinic visits.
	Updated footnote in Table 4 to state that the last dose of study intervention may occur [REDACTED].	[REDACTED]
	Applied corrections to comments for inclusion/exclusion criteria and the Pre-PSG Questionnaire (Table 3) and to the definition of Day 1 (Table 4). Clarified in Table 4 [REDACTED] that pregnancy tests administered after the Screening Visit will be urine pregnancy tests (or per local regulations).	Corrections. Clarification.
[REDACTED]	[REDACTED]	[REDACTED]
4.3 Justification for Dose	Updated section to include titration instructions from the PM.	Text from the PM was added to reflect the inclusion of Canadian participants in the study.
5.2 Exclusion Criteria	Updated exclusion criterion 15 to state that the criterion does not apply to those who have participated in a different study of XYWAV.	Participants who enroll in JZP258-407, a Phase 4, open-label study of an approved treatment (XYWAV), will be taking XYWAV at study entry. Therefore, no increased risk is anticipated for participants who enroll directly into this study from another study of XYWAV.
9.1 Statistical Hypotheses	Updated section to state that formal hypothesis testing will be conducted using the Completer Set.	Updated text to align with updates to Section 9.2.

Section # and Name	Description of Change	Brief Rationale
9.2 Analysis Sets	Added purpose of the Enrolled Set; renamed the Intent-to-Treat Set to the Effectiveness Set and the Modified Intent-to-Treat Set to the Completer Set.	To clarify and align analysis set definitions with definitions in the current SAP.
Sponsor Signatory	Updated the sponsor signatory.	Update.
Throughout the protocol	Added references to the XYWAV PM where appropriate.	Text was added to reflect the inclusion of Canadian participants in the study.

TABLE OF CONTENTS

TITLE PAGE	1
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	2
TABLE OF CONTENTS	5
LIST OF TABLES	9
LIST OF FIGURES	9
LIST OF ABBREVIATIONS	10
1. STUDY SUMMARY	15
1.1. Synopsis	15
1.2. Schema	26
1.3. Schedules of Activities	28
2. INTRODUCTION	42
2.1. Study Rationale	42
2.1.1. Overall Rationale for the Study	42
2.1.2. [REDACTED]	43
2.1.2.1. Existing Elements of Prescribing Information	43
2.1.2.2. [REDACTED]	44
2.1.2.3. [REDACTED]	44
2.2. Background	44
2.3. Benefit/Risk Assessment	45
2.3.1. Risk Assessment	45
2.3.2. Benefit Assessment	46
2.3.3. Overall Benefit/Risk Summary	46
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS	48
4. STUDY DESIGN	54
4.1. Overall Design	54
4.2. Scientific Rationale for Study Design	57
4.2.1. Patient Input Into Design	58
4.3. Justification for Dose	59
4.4. End of Study Definition	59
5. STUDY POPULATION	60
5.1. Inclusion Criteria	60

5.2.	Exclusion Criteria	62
5.3.	Lifestyle Considerations	64
5.4.	Screen Failures.....	65
5.5.	Criteria for Temporarily Delaying Administration of Study Intervention	65
6.	STUDY INTERVENTION(S) AND CONCOMITANT THERAPY.....	66
6.1.	Study Intervention(s)/Treatment(s) Administered.....	66
6.2.	Preparation/Handling/Storage/Accountability.....	68
6.3.	Assignment to Study Intervention	68
6.4.	Blinding/Masking	69
6.5.	Study Intervention/Treatment Compliance.....	69
6.6.	Dose Modification	69
6.7.	Continued Access to Study Intervention After the End of the Study	70
6.8.	Treatment of Overdose, Medication Errors, or Misuse	70
6.9.	Concomitant Therapy	70
7.	DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	72
7.1.	Permanent Discontinuation of Study Intervention	72
7.2.	Participant Discontinuation/Withdrawal From the Study.....	72
7.3.	Lost to Follow-up	73
8.	STUDY ASSESSMENTS AND PROCEDURES.....	74
8.1.	General Administrative Procedures	74
8.1.1.	Informed Consent	74
8.1.2.	Inclusion and Exclusion Criteria Review	74
8.1.3.	Assignment of Participant Number	74
8.1.4.	Medical History	75
8.1.5.	Medication Review (Prior and Concomitant Medications).....	75
8.1.6.	Timing of Study Intervention Dosing.....	75
8.1.7.	Participant/Site Check-In.....	75
8.2.	Efficacy Assessments	76
8.2.1.	Actigraphy	76
8.2.2.	Sleep Diary	76
8.2.3.	Cataplexy Diary (Narcolepsy Type 1 Only).....	76
8.2.4.	Study Intervention Dosing Diary.....	77

8.2.5.	Clinician-Reported Dosing Form	77
8.2.6.	Epworth Sleepiness Scale	78
8.2.7.	Idiopathic Hypersomnia Severity Scale (Idiopathic Hypersomnia Cohort Only)	78
8.2.8.	Narcolepsy Severity Scale (Narcolepsy Cohort Only)	78
8.2.9.	Patient Global Impression of Severity	78
8.2.10.	Patient Global Impression of Change	78
8.2.11.	British Columbia Cognitive Complaints Inventory	78
8.2.12.	Orthostatic Hypotension Questionnaire	79
8.2.13.	Pre-Polysomnography Questionnaire	79
8.2.14.	Polysomnography	79
8.2.15.	Karolinska Sleepiness Scale	80
8.2.16.	Psychomotor Vigilance Test	80
8.2.17.	Functional Outcomes of Sleep Questionnaire-10	80
8.2.18.	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem	81
8.2.19.	Patient Health Questionnaire-9	81
8.3.	Safety Assessments	81
8.3.1.	Physical Examinations	81
8.3.2.	Vital Signs	82
8.3.3.	Apnea/Hypopnea Index	82
8.3.4.	Pulse Oximetry	82
8.3.5.	Electrocardiography	83
8.3.6.	Clinical Safety Laboratory Assessments	83
8.3.7.	Alcohol and Drug Screen	83
8.3.8.	Pregnancy Testing	83
8.3.9.	Suicidal Ideation and Behavior Risk Monitoring	84
8.3.10.	Brief Neurologic Examination	84
8.4.	Adverse Events, Serious Adverse Events, and Other Safety Reporting	84
8.4.1.	Time Period and Frequency for Collecting AE and SAE Information	85
8.4.2.	Method of Detecting AEs and SAEs	85
8.4.3.	Follow-up of AEs and SAEs	85
8.4.4.	Regulatory Reporting Requirements for SAEs	86

8.4.5.	Pregnancy	86
8.5.	Pharmacokinetics	87
8.6.	Pharmacodynamics	87
8.7.	Genetics	87
8.8.	Biomarkers.....	87
8.9.	Immunogenicity Assessments	87
8.10.	Medical Resource Utilization and Health Economics	87
9.	STATISTICAL CONSIDERATIONS	88
9.1.	Statistical Hypotheses	88
9.2.	Analysis Sets.....	88
9.3.	Statistical Analyses	89
9.3.1.	General Considerations.....	89
9.3.2.	Endpoints	89
9.4.	Interim Analysis.....	90
9.5.	Subgroup Analyses	90
9.6.	Sample Size Determination	90
9.7.	Clinician and Patient-Reported Outcomes.....	91
9.8.	Missing Data	91
10.	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS.....	92
10.1.	Regulatory, Ethical, and Study Oversight Considerations	92
10.1.1.	Regulatory and Ethical Considerations	92
10.1.2.	Financial Disclosure	92
10.1.3.	Informed Consent Process	93
10.1.4.	Data Protection	93
10.1.5.	Committees Structure	94
10.1.6.	Dissemination of Clinical Study Data	94
10.1.7.	Data Quality Assurance	94
10.1.8.	Source Documents	95
10.1.9.	Study and Site Start and Closure	95
10.1.9.1.	First Act of Recruitment	95
10.1.9.2.	Study/Site Termination.....	95
10.1.10.	Publication Policy	96

APPENDIX 1. REFERENCES	97
APPENDIX 2. CLINICAL LABORATORY TESTS	101
APPENDIX 3. AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING.....	103
APPENDIX 4. CONTRACEPTIVE AND BARRIER GUIDANCE	109
APPENDIX 5. PROTOCOL AMENDMENT HISTORY	111
INVESTIGATOR AGREEMENT.....	118
SPONSOR SIGNATORY	119

LIST OF TABLES

Table 1: Objectives, Endpoints, and Estimands.....	16
Table 2: Overall Study Design.....	23
Table 3: Schedule of Assessments (Participants With IH or Narcolepsy Who Titrate XYWAV Up To 9 Grams Nightly)	29
Table 4: Schedule of Assessments (> 9-Gram Cohort: Participants With Narcolepsy Who Titrate XYWAV to > 9 Grams to 12 Grams Nightly)	34
Table 5: Schedule of Activities for Participants During the Overnight PK Visit (Twice Nightly Dosage/Narcolepsy)	41
Table 6: Study Treatment/Intervention.....	67
Table 7: Protocol-Required Safety Laboratory Tests	101

LIST OF FIGURES

Figure 1: Study Entry Flow Diagram for Narcolepsy Cohorts	27
---	----

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AASM	American Academy of Sleep Medicine
AE	Adverse event
AHI	Apnea/Hypopnea Index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC _∞	Area under the concentration-time curve from time 0 to infinity
AUC _t	Area under the concentration-time curve from time 0 to last measurable concentration
BC-CCI	British Columbia Cognitive Complaints Inventory
BMI	Body mass index
BP	Blood pressure
BT	Body temperature
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Drug clearance
C _{max}	Maximum plasma concentration
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRF/eCRF	Case report form/Electronic case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
DBP	Diastolic blood pressure

Abbreviation or Term	Definition/Explanation
DNS	Disrupted nighttime sleep
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram/Electrocardiography
ED	Early Discontinuation (Visit)
eDiary	Electronic diary
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EoT	End of Treatment (Intervention)
ESS	Epworth Sleepiness Scale
EU	European Union
FDA	US Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire-10
GABA	Gamma-aminobutyric acid
GHB	Gamma-hydroxybutyrate
h	Hour(s)
hCG	Human chorionic gonadotropin
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICSD	International Classification of Sleep Disorders
ICSD-2	International Classification of Sleep Disorders, Second Edition
ICSD-3	International Classification of Sleep Disorders, Third Edition
IEC	Independent Ethics Committee
IH	Idiopathic hypersomnia
IHSS	Idiopathic Hypersomnia Severity Scale

Abbreviation or Term	Definition/Explanation
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
KSS	Karolinska Sleepiness Scale
m	Minute(s)
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MSLT	Multiple Sleep Latency Test
NA	Not applicable
NOAEL	No observable adverse effect level
NSS	Narcolepsy Severity Scale
NT1	Type 1 narcolepsy
NT2	Type 2 narcolepsy
OHQ	Orthostatic Hypotension Questionnaire
ORE	Other Reportable Experience
OSA	Obstructive sleep apnea
PE	Physical examination
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic(s)
PM	Canadian Product Monograph
PRO	Patient-reported outcome
PSG	Polysomnography
PVT	Psychomotor Vigilance Test
RBC	Red blood cell
REM	Rapid eye movement

Abbreviation or Term	Definition/Explanation
REMS	Risk Evaluation and Mitigation Strategy
REM%	Percentage rapid eye movement (sleep)
RR	Respiration rate
RSG	RAVE Safety Gateway
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System (Institute)
SBP	Systolic blood pressure
SD	Standard deviation
SDP	Stable Dose Period
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
SpO ₂	Oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
SWS	Slow wave sleep
SWS%	Percentage slow-wave sleep
t _½	Half-life
TEAE	Treatment-emergent adverse event
Telecom	Telecommunication
T _{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
TST	Total sleep time
ULN	Upper limit of normal
US	United States (of America)
USPI	United States prescribing information
V	Visit
V/F	Volume of distribution
w	Week(s)

Abbreviation or Term	Definition/Explanation
WASO	Wakefulness after sleep onset
WBC	White blood cell
WOCBP	Women of childbearing potential
WPAI:SHP	Work Productivity and Activity Impairment: Specific Health Problem

1. STUDY SUMMARY

1.1. Synopsis

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

Brief Title: An Open-Label Study to Investigate the Effect of XYWAV on Sleepiness, Polysomnography, and Functional Outcomes in Participants With Idiopathic Hypersomnia or Narcolepsy

Regulatory Agency Identifier Number(s): IND 049641

Rationale: The purpose of this study is to prospectively evaluate XYWAV[®] treatment on daytime and nighttime symptoms in participants with IH or narcolepsy (Type 1 or Type 2). XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution was developed as a low-sodium formulation of XYREM[®] (sodium oxybate) oral solution (XYREM USPI; XYREM PM) and contains the same active moiety, oxybate (GHB), at the same concentration (0.413 g/mL) as XYREM. This study will contribute medical and scientific information relative to XYWAV treatment for patients with IH or narcolepsy. XYWAV was approved in the US for the treatment of IH in adults, based on the results of a Phase 3 study (XYWAV USPI; Dauvilliers, 2022). XYWAV was also approved for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy (in the US) and the treatment of cataplexy in patients with narcolepsy (in Canada), based on the results of a Phase 3 study (XYWAV USPI; XYWAV PM; Bogan, 2021). [REDACTED]

[REDACTED]

[REDACTED]

Potential participants (IH and narcolepsy) who are currently taking an oxybate medication will undergo a 2-week Washout Period before entering the Baseline Period. This will provide a common, non-oxybate treatment baseline whether a participant is on an oxybate medication or is naïve to oxybate.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Objectives, Endpoints, and Estimands:

Table 1: Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary: Idiopathic Hypersomnia (IH) and Narcolepsy		
To evaluate excessive daytime sleepiness in participants with IH or narcolepsy treated with XYWAV	<ul style="list-style-type: none"> ESS total score^a 	<p>Population: Adult participants (18 to 75 years of age) with a primary diagnosis of IH or narcolepsy regardless of oxybate use status (ie, oxybate naïve, current users, or prior users) who reach and complete a 2-week Stable Dose Period of treatment.</p> <p>Treatment: Open-label XYWAV treatment (during the Intervention Period)</p> <p>Intercurrent events: In accordance with a treatment policy strategy, all measurements will be included in the primary analysis regardless of the use of additional or alternative therapies during the Intervention Period.</p> <p>Population-Level Summary: Observed values at each visit, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p>
Secondary: IH and Narcolepsy		
To evaluate safety in participants with IH or narcolepsy treated with XYWAV	<ul style="list-style-type: none"> Incidence and/or severity of washout-emergent AEs and treatment-emergent AEs C-SSRS 	<p>Population: Participants with IH or narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary: Occurrence of AEs will be summarized as count and percentage of participants throughout the study and separately during each study period (eg, Washout Period, [REDACTED]).</p> <p>The C-SSRS item and domain summary indicator values at each clinic visit and specified virtual visits will be summarized as categorical variables (count and percentage).</p>

Objectives	Endpoints	Estimands
Secondary: IH		
To evaluate the participant-reported symptom severity and functional outcomes in participants with IH treated with XYWAV	<ul style="list-style-type: none"> • IHSS total score^a • PGI-C (overall, sleep inertia, fatigue) • Level of rested or refreshed upon awakening (self-report from Sleep eDiary) • PGI-S (overall, sleep inertia, fatigue) 	<p>Population: Participants with IH (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>PGI-C: Response at EoT will be summarized as a categorical variable (count and percentage).</p> <p>eDiary and PGI-S: Responses at each visit and shifts from baseline will be summarized as categorical variables (count and percentage).</p> <p>IHSS: Observed values at each visit and change from baseline will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p>
Secondary: Narcolepsy		
To evaluate PSG measurements in participants with narcolepsy treated with XYWAV	<ul style="list-style-type: none"> • Number of stage shifts from stages N1, N2, and N3, and REM sleep to wake and from stages N2, N3, and REM sleep to N1^a • Duration and percentage of stages N1, N2, and N3^a, and REM sleep • Number of nocturnal arousals • Number of nocturnal awakenings^a 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>Observed values at each visit, change from naïve/washout baseline, [REDACTED]</p> <p>[REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p> <p>Scatterplot and correlation statistics with data pooled across visits will be provided for the absolute value of ESS total score and each PSG parameter.</p> <p>Scatterplot and correlation statistics will be provided for change from baseline to EoT in ESS total score and change from baseline in each PSG endpoint.</p>
To evaluate participant-reported symptom severity and functional outcomes in participants with	<ul style="list-style-type: none"> • PGI-C (overall, sleep inertia, fatigue) • Level of rested or refreshed upon awakening (self-reported from Sleep eDiary) 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p>

Objectives	Endpoints	Estimands
narcolepsy treated with XYWAV	<ul style="list-style-type: none"> PGI-S (overall, sleep inertia, fatigue) 	<p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>PGI-C: Response at EoT will be summarized as a categorical variable (count and percentage).</p> <p>eDiary and PGI-S: Responses at each visit and shift tables from baseline will be summarized as categorical variables (count and percentage).</p>
To evaluate PK characteristics in participants with narcolepsy treated with XYWAV	<p>PK parameters including, but not limited to:</p> <ul style="list-style-type: none"> C_{max} T_{max} $t_{1/2}$ CL/F V/F AUC_t AUC_{∞} 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) who complete a PK Visit (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>Continuous variable summaries for each parameter will be provided.</p>
To evaluate safety in a cohort of participants with narcolepsy treated with XYWAV undergoing a PK Visit	<ul style="list-style-type: none"> Vital signs (BP, HR, BT, RR) Clinical laboratory test results ECG (eg, abnormal ECG findings) Pulse oximetry results 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) who complete a PK Visit (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>Vital signs and clinical laboratory test results: Observed values, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p> <p>Vital signs and pulse oximetry results: Observed values and change from predose baseline will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p> <p>ECG: Observed values at each visit, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum). Abnormal findings at each visit and shifts from naïve/washout baseline and 9-gram baseline (> 9-gram</p>

Page 19

Page 20

Abbreviations: AE = adverse event; AUC_∞ = area under the concentration-time curve from time 0 to infinity;

$C_{\max}$ = maximum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiography; eDiary = electronic diary; EDS = excessive daytime sleepiness; EoT = end of treatment; ESS = Epworth Sleepiness Scale; FOSQ 10 = Functional Outcomes of Sleep Questionnaire-10; REM = rapid eye movement; RR = respiration rate; $t_{1/2}$ = half-life; $T_{\max}$ = time to maximum plasma concentration; V/F = oral volume of distribution;

^a These endpoints are included in the hierarchical testing strategy (refer to Section 9.1).

Brief Summary: This is a prospective, multicenter, single-arm, open-label interventional study of participants with IH or narcolepsy (Type 1 or Type 2). The study duration for each participant (from signing the ICF until the end of the Safety Follow-up Period) will be variable dependent upon the duration of the Screening Period (including the necessity of a medication Washout Period), the duration of the Titration Period, and whether a participant begins in one narcolepsy cohort and ends the study in another. The study will use a single-arm design to evaluate the impact of treatment with XYWAV on sleepiness, PSG measurements (eg, sleep stage transitions, sleep patterns, and sleep quality), daytime and nighttime symptoms, PK (in narcolepsy), and PROs that include subjective sleep quality and quality of life. [REDACTED]

[REDACTED] The single-arm design is adequate for the objectives of this study, as the efficacy of XYWAV treatment has been established previously in randomized controlled Phase 3 studies of participants with IH or narcolepsy, which formed the basis for US approval of XYWAV for these medical conditions. Eligible male and female participants will be 18 to 75 years of age with a primary diagnosis of IH or narcolepsy (Type 1 or Type 2). Participants may be taking oxybate (XYWAV, XYREM[®], or other oxybate medication) at study entry, be oxybate naïve, or have previously taken an oxybate medication. All participants who are taking an oxybate medication at a total nightly dose of ≤ 9 grams at study entry (ie, Visit 1/Screening) will be required to undergo a 2-week Washout Period of their oxybate medication before [REDACTED]

[REDACTED]. Participants may take antiepileptics and/or alerting agents when dosages of these medications have been stable for at least 1 month at the time of study entry and are anticipated to remain stable for the duration of the study, including any washout periods if applicable.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Overall Design:

This is a prospective, multicenter, single-arm, open-label interventional study of participants with IH or narcolepsy (Type 1 or Type 2). In regions where XYWAV follows approved labeling, the protocol is for a Phase 4 interventional study, and in regions where XYWAV does not follow approved labeling, the protocol is for a Phase 3 study.

Table 2: Overall Study Design

Study Phase	Phase 3/Phase 4
Clinical Indication	Treatment for IH or narcolepsy
Study Type	Prospective, open-label, single-arm, multicenter
Type of Control	None
Study Blinding	Not applicable (open-label)
Population	<p>Participants with IH or narcolepsy (Type 1 and Type 2)</p> <p>This study will include participants 18 to 75 years of age (inclusive) with a primary diagnosis of IH or narcolepsy (Type 1 or Type 2). Participants with IH must meet ICSD-3 criteria; participants with narcolepsy must meet ICSD-3 or DSM-V criteria.</p> <p>Participants may either be taking oxybate (XYWAV or XYREM, or other oxybate medication) at study entry, be oxybate naïve, or have previously taken oxybate, with or without additional anticataplectics and/or alerting agents.</p> <p>██████████ cohorts in this study:</p> <p>Idiopathic Hypersomnia Cohort: Baseline assessments are with the participant off oxybate treatment; participants may titrate XYWAV up to 9 grams nightly and there are no PK assessments.</p> <p>Narcolepsy Cohort: Baseline assessments are with the participant off oxybate treatment; participants may titrate XYWAV up to 9 grams nightly and a subset of up to 12 participants will complete optional PK assessments at EoT (V4a).</p> <p>██</p> <p>██</p> <p>██</p> <p>██</p> <p>██</p> <p>██</p> <p>██</p>

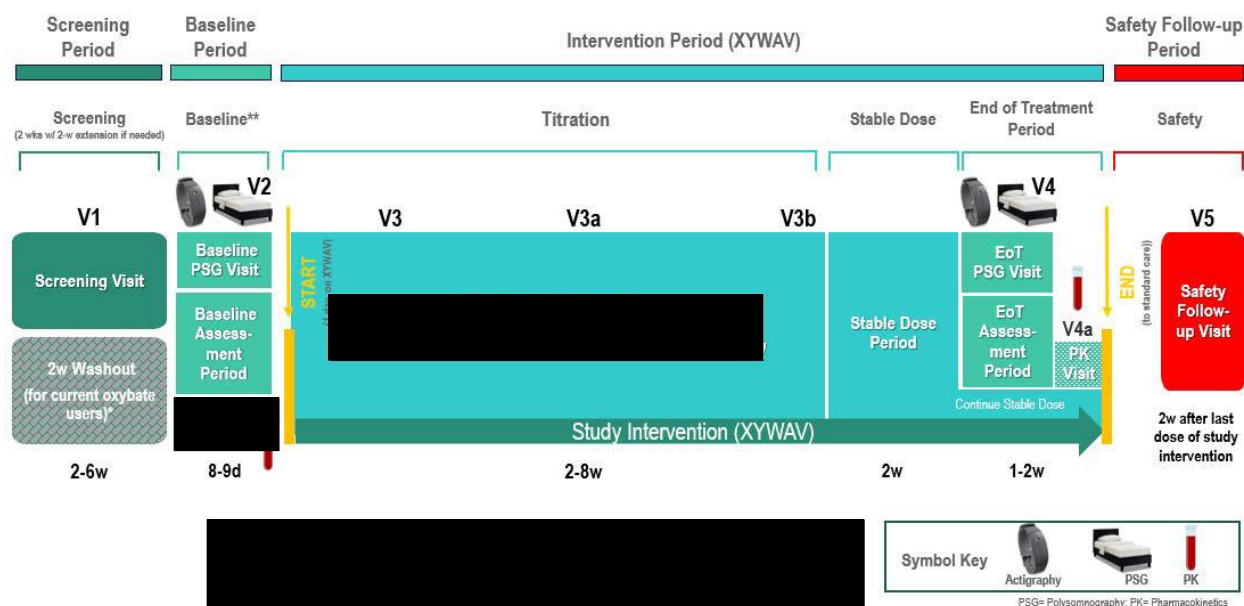
Page 24

	██████████ The duration also reflects flexible time during the Screening Period to accommodate individual schedules and the completion of all screening procedures.
Treatment Duration	5 to 12 weeks ██████████ (depending on the length of the Titration Period, completion of the PK assessments, ██████████ ██████████ ██████████)
Visit Frequency	Up to 17 visits ██████████ (including telemedicine visits and weekly Titration Check-ins via telecom [if not in clinic] during the Flexible Titration Period).
Number of Treatment Arms	1
Treatment Groups	1
Data Monitoring Committee	None planned

Abbreviations: DSM-V = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EoT = End of Treatment (Period); ICF = informed consent form; ICSD-3 = 3 International Classification of Sleep Disorders, Third Edition; IH = idiopathic hypersomnia; PSG = polysomnography.

1.2. Schema

The overall study schema is displayed graphically below:



Abbreviations: EoT = end of treatment; IH = idiopathic hypersomnia; PK = pharmacokinetic(s); PSG = polysomnography; w, wk = week(s); d = day(s); V = visit.

Note: Participants should be reminded to bring any treatment that they typically use at night (eg, continuous positive airway pressure machine, oral device, or medication) to the clinic for overnight study visits. The collection of blood samples for PK assessments may be performed at only select study sites. In addition, PK assessments will not be completed during the same overnight study visit as PSG assessments. The Titration Period is flexible on the basis of investigator judgment (2 to 8 weeks); V3a and V3b are optional and dependent upon the duration of each participant's Titration Period. During the Titration Period, participants will attend weekly Titration Check-in Visits via telecom or in clinic.

As is customary with XYWAV titration, prudent clinical judgment may warrant participants remaining at a given dosage for more than 1 week. Under in-clinic and outpatient supervision of the investigator, increases and/or decreases in dosage are permitted during titration as warranted, with the goal of reaching an optimized balance of efficacy and tolerability.

[REDACTED]

[REDACTED]

[REDACTED]

1.3. Schedules of Activities

Schedules of activities and assessments are provided below for the following populations and cohorts of participants:

- Idiopathic Hypersomnia Cohort: IH population treated with XYWAV up to 9 grams nightly (Table 3).
- Narcolepsy Cohort: Narcolepsy population treated with XYWAV up to 9 grams nightly (Table 3). A subset of up to 12 participants in the narcolepsy cohort who complete the EoT PSG Visit may choose to return to the study site for an optional overnight PK Visit while still taking their stable dose of XYWAV (see Table 5). Confirmation of consent should be verified before the participant proceeds to the PK Visit.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

During the Flexible Titration Period, and in addition to the study visits specified in the SoA (V3, V3a, and V3b in Table 3 [REDACTED]), investigators will perform weekly Titration Check-ins and complete a Clinician-Reported Dosing Form each week (refer to Section 8.2.5). Therefore, participants could have up to 6 Titration Check-ins (starting the day after the participant takes their first dose of study intervention) and up to 3 study visits during the Flexible Titration Period.

- For participants in the IH or narcolepsy cohorts, these weekly Titration Check-ins may occur via telecom.

[REDACTED]
[REDACTED]
[REDACTED]

Participants will start SDP when they achieve an optimized dose as a continuation of the clinic visit (V3, V3a, or V3b in Table 3 [REDACTED]).

Table 3: Schedule of Assessments (Participants With IH or Narcolepsy Who Titrate XYWAV Up To 9 Grams Nightly)

Procedures Day 1 = first day of study intervention. Gray shading indicates virtual visit (telecom) or participant activities at home (SDP)	Screening ^a Period (2 to 6 w)	Baseline Period ^b (8 d)		Intervention Period (5 to ~ 12 w)									ED ^c	Safety Follow-up Period (2 w)	Notes ^a All screening assessments should be done on the same day. ^b If PSG must be repeated (eg, power outage), the sponsor must be contacted, and a repeat PSG must occur within 5 days of the initial PSG. ^c The ED Visit should occur as soon as possible after last study dose of XYWAV (or preferably while still on treatment). ^d EoT is Visit 4 PSG for participants not attending Visit 4a (optional PK Visit). For narcolepsy participants completing the PK Visit, the EoT Period may be closer to 2 weeks in duration. ^e Scheduled days are relative to Day 1, the end of titration, the start of the SDP, or the last dose of study intervention. ^f Weekly Titration Check-ins on Days 21, 28, 42, and 49 (±3) are optional, depending on the titration duration. ^g Last dose may occur at V4, V4a, or ED. ^h If more time is needed due to PSG scheduling, duration of completion of EoT diaries can be extended for 3 days.
				Flexible Titration Period (2 to 8 w) V3a and V3b are optional. Participants can proceed to SDP after V3, V3a, or V3b (depending on the duration of titration).					SDP (2 w)	End of Treatment Period ^b (1 to 2 w)					
Study Visit	Screening Visit	Start	End	Start Titration Check-in	Titration Duration Includes Weekly Titration Check-ins on Days 7, 21, 28, 42, 49 (± 3) ^f				—	Start	End ^d			Safety Follow-up Visit	
	V1	—	V2 PSG	—	Weekly Titration Check-in ^f	V3	V3a	V3b	—	—	V4 PSG	V4a Optional PK		V5	
Scheduled Day(s): ^e	– 21	– 8	– 1	2	7 ^f	14	35	56	—	15	23	24		14	
Relative to:	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	End of Titration	Start of SDP	Start of SDP	Start of SDP		Last ^g Dose	
Study Visit Window (Days)	– 28	– 3	—	—	± 3	± 3	± 3	± 3	—	+ 5 ^h	+ 3	+ 6		+ 3	
Informed consent	X														
Inclusion/Exclusion criteria	X		X/am												
Demographics	X														
Medical history	X	X	X/pm												
Concomitant medication	X	X	X/pm	X	X	X	X	X	X	X	X/pm	X	X	X	
AE/SAE review	X	X	X/pm	X	X	X	X	X	X	X	X/pm	X	X	X	
Physical examination	X														
Height and weight	X		X/pm								X/pm	X	X		
Vital signs (BP, HR, BT, RR)	X		X/pm								X/pm	X	X		
ECG (12-lead)	X											X			
Clinical laboratory tests	X											X			
Breath alcohol test	X		X/pm									X			
Urine drug screen	X											X			

Procedures Day 1 = first day of study intervention. Gray shading indicates virtual visit (telecom) or participant activities at home (SDP)	Screening ^a Period (2 to 6 w)	Baseline Period ^b (8 d)		Intervention Period (5 to ~ 12 w)									ED ^c	Safety Follow- up Period (2 w)	Notes ^a All screening assessments should be done on the same day. ^b If PSG must be repeated (eg, power outage), the sponsor must be contacted, and a repeat PSG must occur within 5 days of the initial PSG. ^c The ED Visit should occur as soon as possible after last study dose of XYWAV (or preferably while still on treatment). ^d EoT is Visit 4 PSG for participants not attending Visit 4a (optional PK Visit). For narcolepsy participants completing the PK Visit, the EoT Period may be closer to 2 weeks in duration. ^e Scheduled days are relative to Day 1, the end of titration, the start of the SDP, or the last dose of study intervention. ^f Weekly Titration Check-ins on Days 21, 28, 42, and 49 (±3) are optional, depending on the titration duration. ^g Last dose may occur at V4, V4a, or ED. ^h If more time is needed due to PSG scheduling, duration of completion of EoT diaries can be extended for 3 days.
				Flexible Titration Period (2 to 8 w) V3a and V3b are optional. Participants can proceed to SDP after V3, V3a, or V3b (depending on the duration of titration).					SDP (2 w)	End of Treatment Period ^b (1 to 2 w)					
Study Visit	Screening Visit	Start	End	Start Titration Check-in	Titration Duration Includes Weekly Titration Check-ins on Days 7, 21, 28, 42, 49 (±3) ^f				—	Start	End ^d			Safety Follow- up Visit	
	V1	—	V2 PSG	—	Weekly Titration Check-in ^f	V3	V3a	V3b	—	—	V4 PSG	V4a Optional PK		V5	
Scheduled Day(s): ^e	– 21	– 8	– 1	2	7 ^f	14	35	56	—	15	23	24		14	
Relative to:	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	End of Titration	Start of SDP	Start of SDP	Start of SDP		Last ^g Dose	
Study Visit Window (Days)	– 28	– 3	—	—	± 3	± 3	± 3	± 3	—	+ 5 ^h	+ 3	+ 6		+ 3	
Pregnancy test (WOCBP only)	X (serum)		X/pm (urine)								X/pm (urine)		X (urine)		Or per local regulations.
C-SSRS (screening/baseline)	X														
C-SSRS (since last visit)		X	X			X	X	X		X	X	X	X	X	
Actigraphy device training and dispense	X		X/pm			X*	X*	X*			X/pm				Participants receive a device after initial eligibility criteria have been met (Screening Visit), on PSG nights, and *after optimized dose is achieved at the start of the SDP (at V3, V3a, or V3b). See Section 8.2.1 .
All eDiary training	X														
Actigraphy data collection		X	X/pm X/am						X	X	X/pm X/am		X		Collect the participant’s device the morning after V2 and V4 PSG.
Sleep eDiary		X	X/am							X	X/am		X		
Cataplexy eDiary (NT1 only)		X	X/pm							X	X/pm		X		
Study intervention dosing diary									X	X	X/am	X	X		
Clinician-reported Dosing Form				X	X	X	X	X							See Section 8.2.5 .

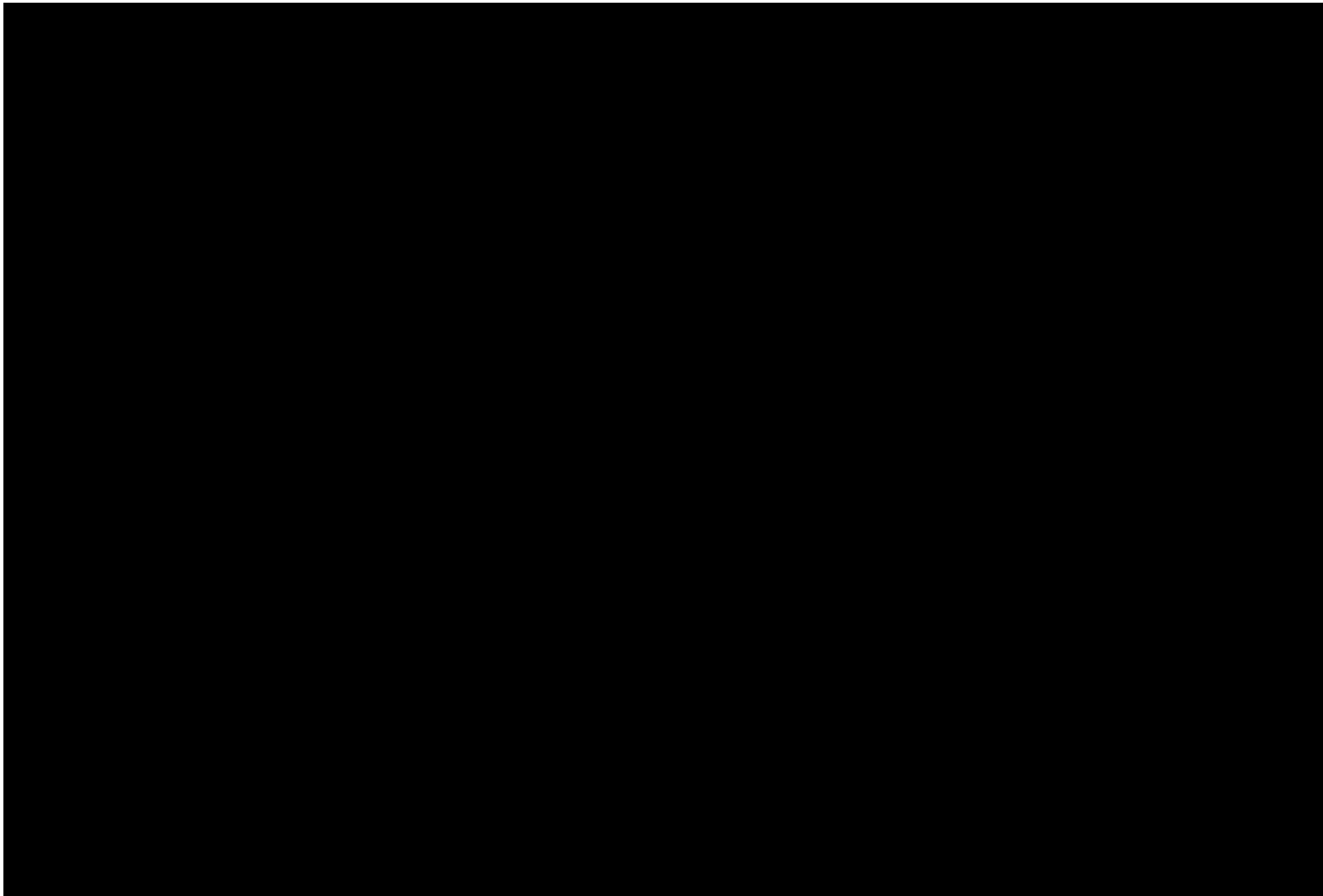
Procedures Day 1 = first day of study intervention. Gray shading indicates virtual visit (telecom) or participant activities at home (SDP)	Screening ^a Period (2 to 6 w)	Baseline Period ^b (8 d)		Intervention Period (5 to ~ 12 w)									ED ^c	Safety Follow- up Period (2 w)	Notes ^a All screening assessments should be done on the same day. ^b If PSG must be repeated (eg, power outage), the sponsor must be contacted, and a repeat PSG must occur within 5 days of the initial PSG. ^c The ED Visit should occur as soon as possible after last study dose of XYWAV (or preferably while still on treatment). ^d EoT is Visit 4 PSG for participants not attending Visit 4a (optional PK Visit). For narcolepsy participants completing the PK Visit, the EoT Period may be closer to 2 weeks in duration. ^e Scheduled days are relative to Day 1, the end of titration, the start of the SDP, or the last dose of study intervention. ^f Weekly Titration Check-ins on Days 21, 28, 42, and 49 (±3) are optional, depending on the titration duration. ^g Last dose may occur at V4, V4a, or ED. ^h If more time is needed due to PSG scheduling, duration of completion of EoT diaries can be extended for 3 days.
				Flexible Titration Period (2 to 8 w) V3a and V3b are optional. Participants can proceed to SDP after V3, V3a, or V3b (depending on the duration of titration).					SDP (2 w)	End of Treatment Period ^b (1 to 2 w)					
Study Visit	Screening Visit	Start	End	Start Titration Check-in	Titration Duration Includes Weekly Titration Check-ins on Days 7, 21, 28, 42, 49 (± 3) ^f				—	Start	End ^d		Safety Follow- up Visit		
	V1	—	V2 PSG	—	Weekly Titration Check-in ^f	V3	V3a	V3b	—	—	V4 PSG	V4a Optional PK		V5	
Scheduled Day(s): ^e	– 21	– 8	– 1	2	7 ^f	14	35	56	—	15	23	24	14		
Relative to:	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	End of Titration	Start of SDP	Start of SDP	Start of SDP	Last ^g Dose		
Study Visit Window (Days)	– 28	– 3	—	—	± 3	± 3	± 3	± 3	—	+ 5 ^h	+ 3	+ 6	+ 3		
ESS	X		X/pm			X	X	X			X/pm		X	The ESS is administered to confirm eligibility (refer to Section 5.1). During the study, the ESS is the first efficacy measure administered, with other efficacy measures administered in the order that they appear in this table.	
IHSS (IH only)			X/pm			X	X	X			X/pm		X		
NSS (narcolepsy only)			X/pm			X	X	X			X/pm		X		
PGI-S (overall, sleep inertia, fatigue)			X/pm			X	X	X			X/pm		X	See Section 8.2.9.	
PGI-C (overall, sleep inertia, fatigue)						X	X	X			X/pm		X		
BC-CCI			X/pm								X/pm		X		
OHQ			X/pm								X/pm		X		
Pre-PSG questionnaire			X/pm								X/pm		X	For ED, only for participants who have titrated XYWAV and completed at least 1 week of the SDP.	
PVT training			X/pm								X/pm		X		
PSG			X/pm X/am								X/pm X/am		X	See Section 8.2.14 for administration parameters and Section 7.2 for ED.	
KSS			X/am								X/am		X	7 times in morning after PSG.	

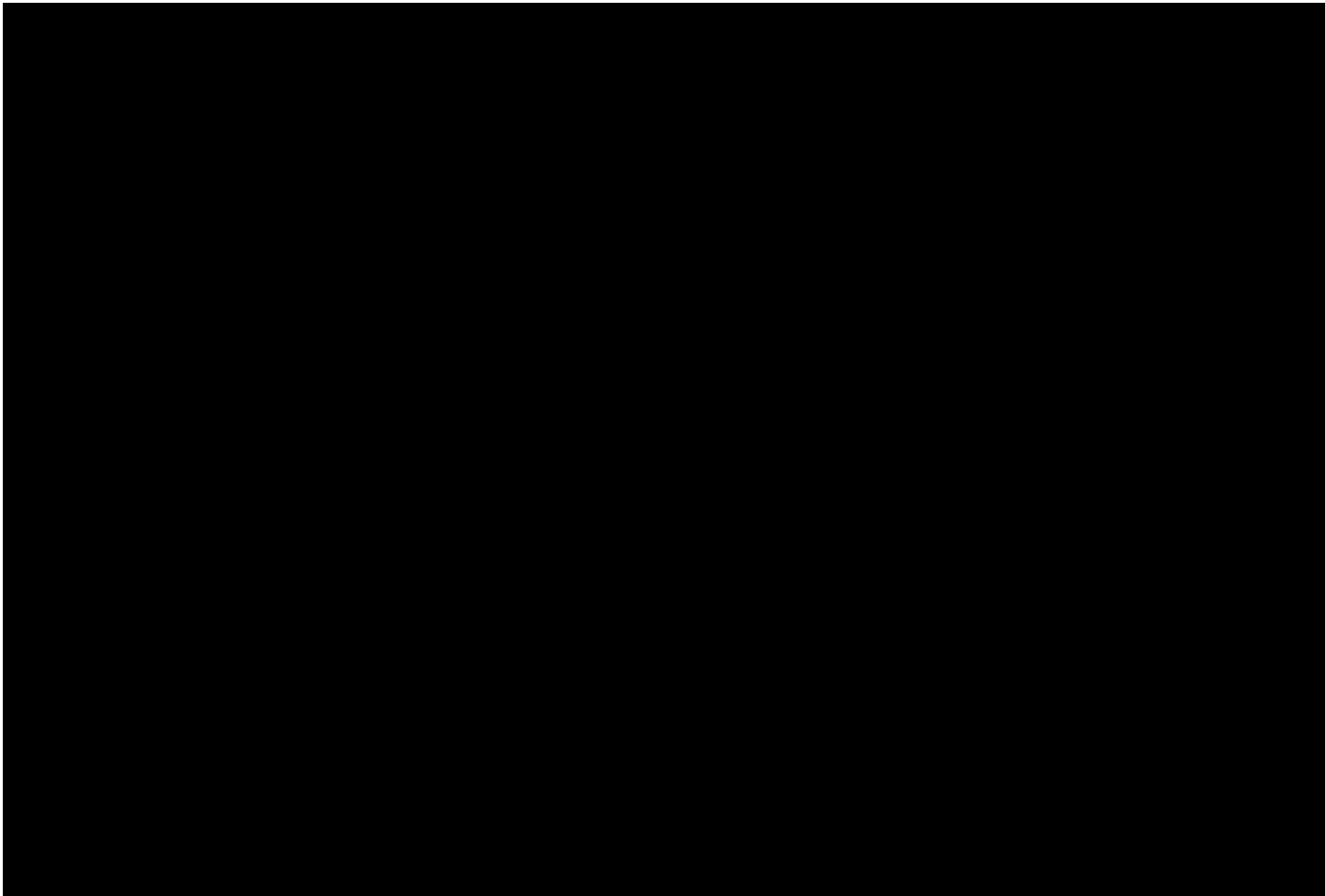
Procedures Day 1 = first day of study intervention. Gray shading indicates virtual visit (telecom) or participant activities at home (SDP)	Screening ^a Period (2 to 6 w)	Baseline Period ^b (8 d)		Intervention Period (5 to ~ 12 w)									ED ^c	Safety Follow- up Period (2 w)	Notes ^a All screening assessments should be done on the same day. ^b If PSG must be repeated (eg, power outage), the sponsor must be contacted, and a repeat PSG must occur within 5 days of the initial PSG. ^c The ED Visit should occur as soon as possible after last study dose of XYWAV (or preferably while still on treatment). ^d EoT is Visit 4 PSG for participants not attending Visit 4a (optional PK Visit). For narcolepsy participants completing the PK Visit, the EoT Period may be closer to 2 weeks in duration. ^e Scheduled days are relative to Day 1, the end of titration, the start of the SDP, or the last dose of study intervention. ^f Weekly Titration Check-ins on Days 21, 28, 42, and 49 (±3) are optional, depending on the titration duration. ^g Last dose may occur at V4, V4a, or ED. ^h If more time is needed due to PSG scheduling, duration of completion of EoT diaries can be extended for 3 days.
				Flexible Titration Period (2 to 8 w) V3a and V3b are optional. Participants can proceed to SDP after V3, V3a, or V3b (depending on the duration of titration).					SDP (2 w)	End of Treatment Period ^b (1 to 2 w)					
Study Visit	Screening Visit	Start	End	Start Titration Check-in	Titration Duration Includes Weekly Titration Check-ins on Days 7, 21, 28, 42, 49 (± 3) ^f				—	Start	End ^d		Safety Follow- up Visit		
	V1	—	V2 PSG	—	Weekly Titration Check-in ^f	V3	V3a	V3b	—	—	V4 PSG	V4a Optional PK	V5		
Scheduled Day(s): ^e	– 21	– 8	– 1	2	7 ^f	14	35	56	—	15	23	24	14		
Relative to:	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	End of Titration	Start of SDP	Start of SDP	Start of SDP	Last ^g Dose		
Study Visit Window (Days)	– 28	– 3	—	—	± 3	± 3	± 3	± 3	—	+ 5 ^h	+ 3	+ 6	+ 3		
PVT (10-minute version)			X/am								X/am		X		3 tests in morning after PSG (with some PSG sensors recording during PVT [see PSG Manual])).
FOSQ-10			X/am								X/am		X		
WPAI: SHP			X/am								X/am		X		
PHQ-9			X/am								X/am		X		
Dispense study intervention (XYWAV)			X/am			X	X	X			X/am				Participants take their first dose of study intervention on Day 1 (refer to Section 4.1). At V4, dispense study intervention only to those participating in Visit 4a (optional PK Visit).
Study intervention compliance review					X	X	X	X		X	X/am	X	X		
Collect study intervention						X	X	X			X/am	X	X		
Participant/Site check- in and instructions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.1.7.
Serial PK blood collection (optional for participants with narcolepsy)												X			See Table 5.
Brief neurologic examination												X			Conducted in the morning prior to discharge. Investigators or qualified study staff will ensure participant is cleared to leave the unit (see Section 8.3.10).

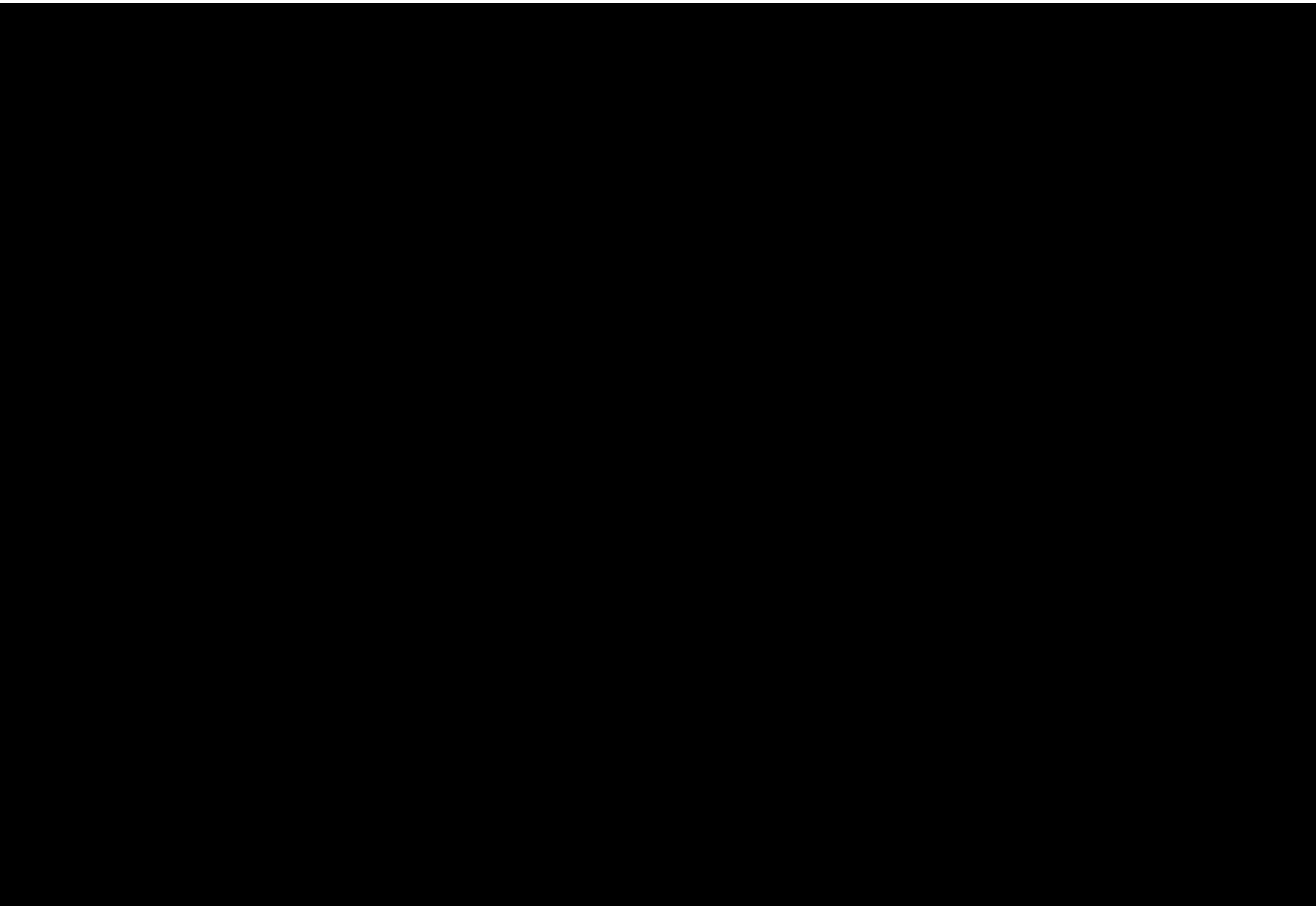
Abbreviations: AE = adverse event; BC-CCI = British Columbia Cognitive Complaints Inventory; BMI = body mass index; BP = blood pressure; BT = body temperature; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day(s); ECG = electrocardiography; ED = Early Discontinuation (Visit); eDiary = electronic diary; EoT = end of treatment; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire-10; HR = heart rate; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; KSS = Karolinska Sleepiness Scale; NSS = Narcolepsy Severity Scale; NT1 = narcolepsy Type 1; OHQ = Orthostatic Hypotension Questionnaire; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic(s); PSG = polysomnography; PVT = Psychomotor Vigilance Test; RR = respiration rate; SAE = serious adverse event; SDP = Stable Dose Period; telecom = telecommunication; V = visit; w = week(s); WOCBP = women of childbearing potential; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.
NOTE: pm = prior to PSG in the evening; am = after PSG in the morning.

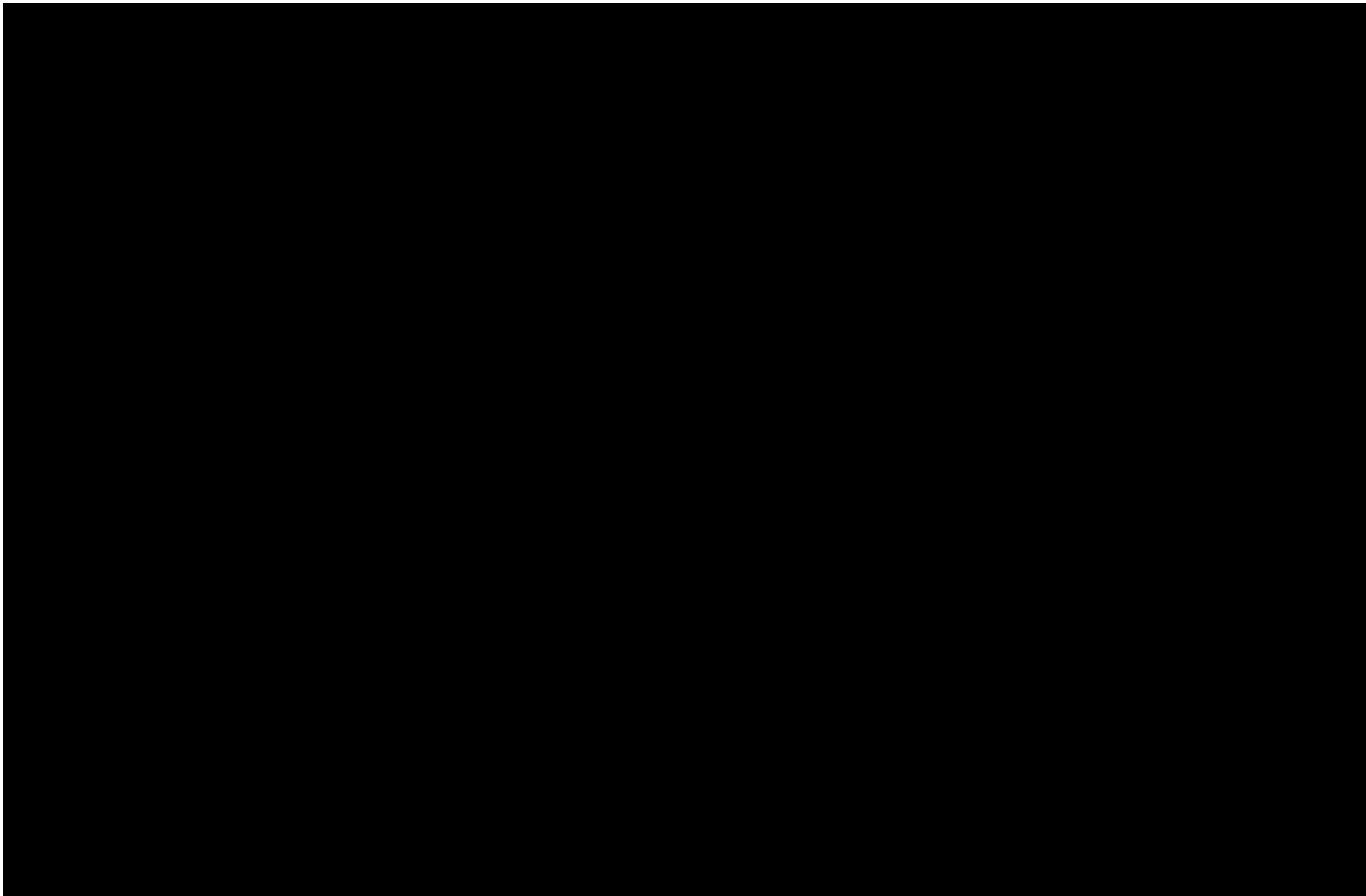
[REDACTED]

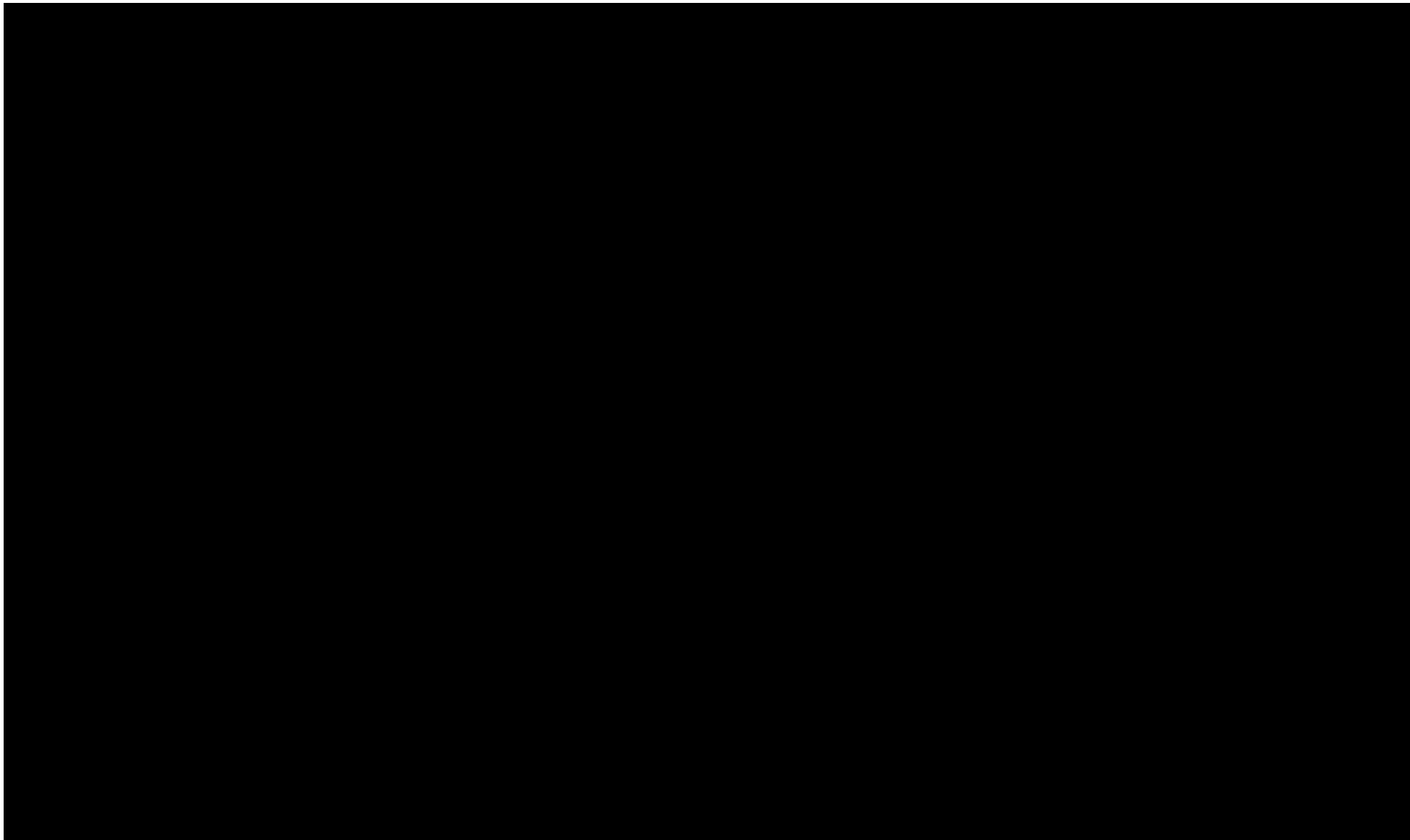
[REDACTED]











The schedule of assessments and other activities for the overnight PK Visit (twice nightly dosage/narcolepsy only) is provided below. The PK assessments will be performed for participants in the narcolepsy cohort who take part in the optional Visit 4a during the EoT Period (see [Table 3](#)).

Table 5: Schedule of Activities for Participants During the Overnight PK Visit (Twice Nightly Dosage/Narcolepsy)

Procedures	Prior to PK Blood Samples (Predose)			PK Time Points ^a																Prior to Discharge	Notes
				First Dose						Second Dose (Administered 4 Hours After First Dose)						6h After 1st Dose	8h After 1st Dose	10h After 1st Dose	12h After 1st Dose		
	- 1.5h ± 15m ^a	- 1h ± 5m	- 30m ± 5m	≤ 15m Predose	1st Dose	0.5h	0.75h	1h	1.5h	≤ 15m Predose	2nd Dose	0.5h	0.75h	1h	1.5h						
Record time of dose					X						X										Supervise XYWAV administration.
Blood samples for PK				X		X	X	X	X	X		X	X	X	X	X	X	X	X		
Vital signs (BP, HR, BT, RR)				X (with BT)		X	X	X	X	X		X	X	X	X	X	X (with BT)	X	X	X	Vital signs measurements are taken before blood collection.
Weight	X																				At check-in (not needed within specified window).
Pulse oximetry				X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	Continuous; record value at times shown along with other vital signs measurements (prior to blood collection).
ECG																				X	Before blood collection for clinical laboratory tests.
Brief neurologic examination																				X	Conducted prior to discharge. Investigators or qualified study staff will ensure participant is cleared to leave the unit (see Section 8.3.10).
AE/SAE review	<-----Continuous Monitoring----->																				

Abbreviations: AE = adverse event; BP = blood pressure; BT = body temperature; ECG = electrocardiography; h = hour(s); HR = heart rate; m = minute(s); PK = pharmacokinetic(s); RR = respiration rate; SAE = serious adverse event.

^a When multiple procedures are scheduled for the same time point, PK blood samples will be taken at the protocol-assigned time point (within ± 2 minutes of the specified time points during the first hour after each dose, and within ± 5 minutes of the specified time points after 1 hour). Other measurements (ie, vital signs and pulse oximetry results) may be taken before or after the protocol-specified time point within a window of ± 15 minutes; however, whenever possible, these measurements should be taken before blood collection.

2. INTRODUCTION

XYWAV[®] (calcium, magnesium, potassium, and sodium oxybates) oral solution (also known as JZP258) was developed as an alternative low-sodium formulation for XYREM[®] (sodium oxybate) oral solution. XYWAV contains the same active moiety, oxybate (GHB), at the same concentration (0.413 g/mL) as XYREM. By formulating oxybate with a mixture of cations, XYWAV has 92% less sodium, or approximately 1000 to 1500 mg/night less sodium, than XYREM in the anticipated dosage range of 6 to 9 grams nightly.

XYWAV is approved in the US and is indicated, as shown in the USPI, for cataplexy or EDS in patients 7 years of age and older with narcolepsy. More recently, approval was also granted in the US for the treatment of IH in adults ([XYWAV USPI](#)). In Canada, XYWAV is approved for the treatment of cataplexy in patients with narcolepsy ([XYWAV PM](#)). Although the precise mechanism of action is not known, it is hypothesized that the therapeutic effects of XYWAV are mediated through neuropharmacologic GABA_B-receptor-mediated actions on noradrenergic and dopaminergic neurons as well as on thalamocortical neurons ([XYWAV USPI](#); [Pardi, 2006](#)). Clinical studies have shown that treatment with sodium oxybate increases slow-wave (delta or restorative) sleep and improves sleep continuity ([Pardi, 2006](#)).

2.1. Study Rationale

2.1.1. Overall Rationale for the Study

This study will prospectively evaluate daytime and nighttime symptoms in participants with IH or narcolepsy (Type 1 or Type 2) treated with XYWAV utilizing assessments of sleepiness, PSG measurements, PK (in narcolepsy), PVT metrics, actigraphy measurements, and other PROs. Excessive daytime sleepiness is common to both IH and narcolepsy; however, these disorders are distinct entities with other symptoms more specific to either IH or to narcolepsy, including self-reported and objective aspects of sleep disturbance and sleep quality ([Maski, 2021a](#)).

The primary objective will address the change in EDS with XYWAV treatment. The efficacy of XYREM, the high-sodium product, on EDS and/or cataplexy in narcolepsy was demonstrated in 4 randomized Phase 3 clinical studies in adults and an additional placebo-controlled randomized-withdrawal study in pediatric patients ([XYWAV USPI Studies 1-4 and 5](#); [XYREM International Study Group 2005](#); [Black, 2006](#)). XYWAV efficacy for cataplexy and EDS in narcolepsy was established in a single Phase 3, placebo-controlled, randomized-withdrawal study ([Bogan, 2021](#)). This Phase 3 study had a randomized-withdrawal study design and demonstrated worsening in cataplexy and EDS when participants were randomly assigned to treatment with placebo, compared with participants randomly assigned to continuing XYWAV treatment. The results of the current study will provide further direct evidence of the positive effect of XYWAV treatment on EDS in adults with narcolepsy. Similarly, the efficacy of XYWAV in IH was shown in a single Phase 3, placebo-controlled randomized-withdrawal study ([Dauvilliers, 2022](#)). The results of the current study will serve to add to the scientific evidence of the effect of XYWAV treatment in people with IH. As a cohort study, the ESS was selected as the primary measure for the assessment of EDS, the key symptom in both hypersomnolence disorders evaluated in this study. The ESS total score has been shown to be significantly improved in double-blind

randomized-withdrawal studies in both IH and narcolepsy populations ([Bogan, 2021](#); [Dauvilliers, 2022](#)).

Other objectives of the current study aim to evaluate the effect of XYWAV treatment on sleep architecture utilizing PSG in the study participants. While studies have shown that XYREM improves nocturnal sleep (eg, increased slow-wave sleep and decreased light sleep and awakenings in narcolepsy) (for details see Section 4.2; [Black, 2009](#); [Black, 2010](#)), no sleep studies to date have been performed with XYWAV in IH or narcolepsy. The results of PSG sleep metrics in this study will further the understanding of the mechanism of disease and the mechanism of action of XYWAV in IH and narcolepsy. The assessment of functional and quality-of-life outcomes in this study will further support the clinical benefit of XYWAV treatment. The potential for correlating PSG outcomes to daytime and nighttime symptom assessments may further support the clinical relevance of findings. Overall, data from this study will provide a better understanding of the impact of sleep quality on patient health, cognition, mood, and health-related quality of life, and will be informative for health care providers choosing between treatment options for patients with IH or narcolepsy.

2.1.2.

[REDACTED]

2.1.2.1. Existing Elements of Prescribing Information

The existing elements of prudent prescribing, titration, and maintenance described in the XYWAV USPI and PM include the following prescribing instructions:

- Adherence to a titration schedule (USPI Section 2.1 and PM Section 4.2)

- Low starting dose accompanied by a gradual titration (USPI Section 2.1 and PM Section 4.2)
- Prohibition of (contraindicated) combination with alcohol and sedative hypnotics (USPI Section 4 and PM Section 2)
- Warning of increased risk with concomitant CNS depressants (USPI Section 5.1 and PM Section 7)
- Consideration of dose reduction if concomitant CNS depressants are required (Section 5.1 and PM Section 7)
- Maintain awareness of participants at increased risk (Section 5.4 and PM Section 7)

2.1.2.2.

[REDACTED]

2.1.2.3.

[REDACTED]

2.2. Background

Narcolepsy is a debilitating life-long neurologic disease for which no cure has been identified. Narcolepsy is characterized by EDS and DNS ([Roth, 2013](#)), and abnormal REM-sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations; narcolepsy may adversely affect quality of life ([Bassetti, 2019](#)).

Idiopathic hypersomnia is also a debilitating central disorder of hypersomnolence (International Classification of Sleep Disorders, Third Edition [ICSD-3]; [AASM, 2014](#)). Symptoms of IH include EDS, prolonged night-time sleep, long unrefreshing naps, and pronounced sleep inertia leading to profound impairment in quality of life and function ([Dauvilliers, 2022](#)). The ICSD,

Second Edition (ICSD-2) describes 2 subtypes of IH, one with night-time long sleep time (> 10 hours of nocturnal sleep) and the other without night-time long sleep time (> 6 but < 10 hours of nocturnal sleep). The current edition of the ICSD (ICSD-3) does not include this distinction; however, diagnostic criteria include either demonstrated long sleep time (≥ 11 hours of 24-hour TST) or demonstrated objective sleepiness (MSLT < 8 minutes) (ICSD-3). Sleep inertia, which is considered an essential feature of IH, is seen in most patients with IH and can be prolonged and severe. Sleep inertia is defined as difficulty waking with automatic behavior, confusion, and repeated returns to sleep; in its severe form, it is sometimes referred to as “sleep drunkenness” (Bassetti, 1997; Anderson, 2007; Trotti, 2017).

There is no consensus regarding consistent PSG pathology in IH. A recent systematic review and meta-analysis concluded that IH is associated with several changes in sleep staging and architecture relative to healthy persons, including alterations in REM and SWS, with increased TST and REM % and decreased sleep onset latency and SWS % (Plante, 2018; see Section 4.2 for further details). Due to the severity of symptoms, IH has profound negative effects on day-to-day functioning, including the ability to sustain employment and overall poor quality of life (Ozaki, 2008; Vernet, 2010; Ozaki, 2012). Idiopathic hypersomnia also poses considerable safety risks, as patients may be more susceptible to accidents at work or while operating a motor vehicle (Pizza, 2015; Ahmed, 2016).

As of March 2023, only XYWAV has been approved in the US for IH. Otherwise, patients are treated on the basis of their symptoms, and medications are prescribed “off-label” in the absence of evidence regarding safety and efficacy (Anderson, 2007; Ozaki, 2008; Lavault, 2011; Nittur, 2013; Trotti, 2015). Better understanding of PSG data may contribute to objective sleep quality parameters for patients with IH or narcolepsy taking XYWAV.

A detailed description of the chemistry, pharmacology, efficacy, and safety of XYWAV is provided in the IB. The prescribing information (ie, USPI and PM) will be used as the Reference Safety Information.

2.3. Benefit/Risk Assessment

A summary of the benefit-risk assessment for conducting this study is provided in the subsections below.

2.3.1. Risk Assessment

Participants who enroll in this study may encounter the following potential risks:

- There are study procedure-related risks, including risks and discomfort associated with blood collection (for clinical laboratory assessments or PK) and data collection from devices (eg, due to EEG/ECG leads, from wearing actigraphy device).
- Adverse effects for participants receiving XYWAV are expected to be similar to those seen in previously conducted clinical studies with XYWAV (detailed in the XYWAV IB, XYWAV USPI, and XYWAV PM).
- Participants entering the study taking oxybate medication may experience worsening of symptoms during the 2-week Washout Period.

- XYWAV is a CNS depressant, and respiratory depression can occur with its use. Therefore, participants will be monitored closely while titrating XYWAV.

[REDACTED]

In controlled clinical studies of adults with narcolepsy or IH, adverse events most commonly reported (in 5% or more participants treated with XYWAV) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, vomiting, insomnia, dry mouth, fatigue, somnolence, and tremor (XYWAV USPI). Treatment with XYWAV may cause CNS depression. Abuse or misuse of XYWAV, either alone or in combination with CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decrease in the level of consciousness, coma, and death. XYWAV is contraindicated for use in combination with sedative hypnotics, in combination with alcohol, and in patients with succinic semialdehyde dehydrogenase deficiency.

Since sodium oxybate (same active moiety as XYWAV) has been marketed, the following additional adverse reactions have been identified: arthralgia, fall (possibly while rising from bed), fluid retention, hangover, hypersensitivity, hypertension, memory impairment, nocturia, and vision blurred.

For further information see XYWAV prescribing information (XYWAV USPI; XYWAV PM).

2.3.2. Benefit Assessment

Participants who enroll in this study may experience the following benefits:

- Possibility of improved symptom control with XYWAV treatment
- Access to comprehensive clinical examinations and clinical monitoring associated with the study (NOTE: Participants will also be provided a personalized end-of-study report sharing results for key study assessments)
- Participant contribution to improving physicians' knowledge when considering treatment choices for patients with IH or narcolepsy, as well as contributing to the understanding of their disease

2.3.3. Overall Benefit/Risk Summary

Benefits to the participants include a comprehensive physical examination, clinical laboratory tests, other medical tests, and access to information collected from study devices and assessments. This is in addition to treatment during the Intervention Period to alleviate symptoms of IH or narcolepsy for those entering the study naïve to oxybate medication.

Risks to the participants include those related to study procedures. These risks are expected to be similar to those seen in previous clinical studies (see Section 2.2). Additional risks include those associated with the administration of XYWAV, which are expected to be similar to those seen in previous clinical studies and in the postmarketing setting. More detailed information about the

known and expected benefits and risks and TEAEs of XYWAV are provided in the USPI and PM ([XYWAV USPI](#); [XYWAV PM](#)).

[REDACTED]

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary: Idiopathic Hypersomnia (IH) and Narcolepsy		
To evaluate excessive daytime sleepiness in participants with IH or narcolepsy treated with XYWAV	<ul style="list-style-type: none"> ESS total score^a 	<p>Population: Adult participants (18 to 75 years of age) with a primary diagnosis of IH or narcolepsy regardless of oxybate use status (ie, oxybate naïve, current users, or prior users) who reach and complete a 2-week Stable Dose Period of treatment.</p> <p>Treatment: Open-label XYWAV treatment (during the Intervention Period)</p> <p>Intercurrent events: In accordance with a treatment policy strategy, all measurements will be included in the primary analysis regardless of the use of additional or alternative therapies during the Intervention Period.</p> <p>Population-Level Summary: Observed values at each visit, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p>
Secondary: IH and Narcolepsy		
To evaluate safety in participants with IH or narcolepsy treated with XYWAV	<ul style="list-style-type: none"> Incidence and/or severity of washout-emergent AEs and treatment-emergent AEs C-SSRS 	<p>Population: Participants with IH or narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary: Occurrence of AEs will be summarized as count and percentage of participants throughout the study and separately during each study period (eg, Washout Period, ≤ 9-gram Titration Period, [REDACTED]).</p> <p>The C-SSRS item and domain summary indicator values at each clinic visit and specified virtual visits</p>

Objectives	Endpoints	Estimands
		will be summarized as categorical variables (count and percentage).
Secondary: IH		
To evaluate the participant reported symptom severity and functional outcomes in participants with IH treated with XYWAV	<ul style="list-style-type: none"> • IHSS total score^a • PGI-C (overall, sleep inertia, fatigue) • Level of rested or refreshed upon awakening (self report from Sleep eDiary) • PGI-S (overall, sleep inertia, fatigue) 	<p>Population: Participants with IH (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>PGI-C: Response at EoT will be summarized as a categorical variable (count and percentage).</p> <p>eDiary and PGI-S: Responses at each visit and shifts from baseline will be summarized as categorical variables (count and percentage).</p> <p>IHSS: Observed values at each visit and change from baseline will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p>
Secondary: Narcolepsy		
To evaluate PSG measurements in participants with narcolepsy treated with XYWAV	<ul style="list-style-type: none"> • Number of stage shifts from stages N1, N2, and N3, and REM sleep to wake and from stages N2, N3, and REM sleep to N1^a • Duration and percentage of stages N1, N2, and N3^a, and REM sleep • Number of nocturnal arousals • Number of nocturnal awakenings^a 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary:</p> <p>Observed values at each visit, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum).</p> <p>Scatterplot and correlation statistics with data pooled across visits will be provided for the absolute value of ESS total score and each PSG parameter.</p> <p>Scatterplot and correlation statistics will be provided for change from baseline to EoT in ESS total score and change from baseline in each PSG endpoint.</p>

Objectives	Endpoints	Estimands
To evaluate participant reported symptom severity and functional outcomes in participants with narcolepsy treated with XYWAV	<ul style="list-style-type: none"> PGI-C (overall, sleep inertia, fatigue) Level of rested or refreshed upon awakening (self-reported from Sleep eDiary) PGI-S (overall, sleep inertia, fatigue) 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary: PGI-C: Response at EoT will be summarized as a categorical variable (count and percentage). eDiary and PGI-S: Responses at each visit and shift tables from baseline will be summarized as categorical variables (count and percentage).</p>
To evaluate PK characteristics in participants with narcolepsy treated with XYWAV	<p>PK parameters including, but not limited to:</p> <ul style="list-style-type: none"> C_{max} T_{max} $t_{1/2}$ CL/F V/F AUC_t AUC_{∞} 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) who complete a PK Visit (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary: Continuous variable summaries for each parameter will be provided.</p>
To evaluate safety in a cohort of participants with narcolepsy treated with XYWAV undergoing a PK Visit	<ul style="list-style-type: none"> Vital signs (BP, HR, BT, RR) Clinical laboratory test results ECG (eg, abnormal ECG findings) Pulse oximetry results 	<p>Population: Participants with narcolepsy (Type 1 and Type 2) who complete a PK Visit (more specifically defined above with primary estimand)</p> <p>Treatment and intercurrent events are defined above with primary estimand.</p> <p>Population-Level Summary: Vital signs and clinical laboratory test results: Observed values, change from naïve/washout baseline, [REDACTED] will be summarized as continuous variables (mean, standard deviation, quartiles, minimum, maximum). Vital signs and pulse oximetry results: Observed values and change from predose baseline will be summarized as continuous variables</p>

[illegible]

Page 52

Abbreviations: AE = adverse event; AUC_{∞} = area under the concentration-time curve from time 0 to infinity; CL/F = oral drug clearance; $C_{\max}$ = maximum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiography; eDiary = electronic diary; EoT = end of treatment; ESS = Epworth Sleepiness Scale; HR = heart rate; IH = idiopathic hypersomnia; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PSG = polysomnography;

^a These endpoints are included in the hierarchical testing strategy (refer to Section 9.1).

4. STUDY DESIGN

4.1. Overall Design

This is a prospective, multicenter, single-arm, open-label interventional study of participants with IH or narcolepsy (Type 1 or Type 2). In regions where XYWAV follows approved labeling, the protocol is for a Phase 4 interventional study, and in regions where XYWAV does not follow approved labeling, the protocol is for a Phase 3 study.

The study duration for each participant (from enrollment [ie, signing the ICF] until the end of the Safety Follow-up Period) will be approximately 10 to 21 weeks [REDACTED] and is dependent upon the duration of the Screening Period (including the necessity of a medication washout period), the duration of the Titration Period, [REDACTED]

The study will use a single-arm design to evaluate the effect of treatment with XYWAV on sleepiness, PSG measurements (eg, sleep stage transitions, sleep patterns, and sleep quality), daytime and nighttime symptoms, PK (in narcolepsy), and PROs that include subjective sleep quality and quality of life. All data collected in this study will be summarized descriptively. The single-arm design is adequate for the objectives of this study, as the efficacy of XYWAV treatment has been established previously in randomized controlled Phase 3 studies of participants with narcolepsy or IH, which formed the basis for the approval of XYWAV for these conditions in the US (XYWAV USPI Studies 15-006 and JZP080-301, respectively).

Eligible male and female participants will be 18 to 75 years of age with a primary diagnosis of IH or narcolepsy (Type 1 or Type 2). Participants may be taking oxybate (XYWAV, XYREM, or other oxybate medication) at study entry, be oxybate naïve, or have previously taken an oxybate medication. Participants who are taking an oxybate medication at study entry will be required to undergo a 2-week Washout Period of their oxybate medication before undergoing baseline assessments [REDACTED].

Participants may take antiepileptics and/or alerting agents when dosages of these medications have been stable for at least 1 month at the time of study entry and are anticipated to remain stable for the duration of the study (unless changes in these medications are required due to safety concerns in the opinion of the investigator).

Participants will proceed through the following study periods:

1. Screening Period (2 to 6 weeks)

- Screening Visit 1 (1 day within a 2- to 4-week window)

The Screening Visit assessments should be performed in 1 day. Although all efforts will be made to have participants complete the Screening Period within 2 weeks, the Screening Period may be extended by an additional 2 weeks, as needed, to accommodate schedules (eg, holidays, travel, transient illness, staff absences, and PSG scheduling) and to review screening information (eg, clinical laboratory test results). Refer to Section 8.1.7 for additional details.

- Washout Period (2-weeks [for current oxybate users only])

After Screening Visit 1, participants currently taking oxybate (eg, XYWAV, XYREM, or other oxybate medication) who are still considered eligible will discontinue their oxybate medication for 2 weeks (ie, washout) before baseline assessments may begin (see [Table 3](#)). Participants will remain off oxybate during the Baseline Period (thus, these participants may be off oxybate treatment for a total of approximately 3 weeks). Study personnel should determine if any sponsor-supported assistance is needed during this time (Section [8.1.7](#)), and washout-emergent AEs should be reported (Section [8.4.1](#)).

2. Baseline Period (8 days for IH cohort and narcolepsy cohort treated with ≤ 9 grams; [REDACTED])

Participants complete some assessments at home (diaries, actigraphy) before attending the Baseline PSG (Visit 2 PSG/ [REDACTED]). Study staff will confirm eligibility for all participants after the Baseline PSG (including a review of the AHI during the Baseline PSG [see exclusion criterion [2](#)]) before dispensing study intervention and before the participant may proceed to the Intervention Period. Refer to Section [8.2.14](#) for additional details.

NOTE: Baseline assessments for participants in the IH and narcolepsy cohorts are performed while the participant is not taking oxybate. [REDACTED]

3. Intervention Period (5 to ~ 12 weeks for IH cohort and narcolepsy cohort treated with ≤ 9 grams [REDACTED])

- Flexible Titration Period (flexible on the basis of investigator judgment [2 to 8 weeks]): IH cohort and narcolepsy cohort who titrate to an optimal dose of XYWAV (to a maximum of 9 grams nightly):

Participants in the IH and narcolepsy cohorts will be instructed to take their first dose of study intervention (ie, Day 1) in the evening (after their eligibility was confirmed earlier that day following the Baseline Visit 2 PSG). Participants will continue their stable dosages of additional antiepileptics and/or alerting agents during this time. XYWAV will be titrated to each participant's optimal dosage as recommended in the [XYWAV USPI](#) and [XYWAV PM](#). Participants will be provided detailed instructions regarding their treatment regimen during the Intervention Period.

Starting the day after the participant's first dose of study intervention, and to better understand clinician dosing rationale, investigators will be asked to perform weekly Titration Check-ins (which may be telecom visits), confirm the participant's optimized dosage, and complete a Clinician-reported Dosing Form to obtain information on the clinician's dosing decisions (see Section [8.2.5](#)). After an optimal dosage is achieved based on the investigator's clinical judgment, participants will proceed to the SDP.

[REDACTED]

- Stable Dose Period (2 weeks)

Participants will maintain their optimized stable XYWAV dosage during this 2-week period and complete study activities at home (no Check-ins or study visits are scheduled during this time). The Participant Dosing eDiary will be completed each morning, and actigraphy device will be worn. Participants will be reminded when to start wearing the actigraphy device and when to start completing the diaries.

- EoT Period (1 to 2 weeks)

- EoT Period (8 days)
- EoT/End V4 PSG (1 night plus morning after)
- EoT Visit 4a PK (1 night/optional for narcolepsy cohort [REDACTED])

During the EoT Period, participants complete some assessments at home (diaries, actigraphy) before attending the EoT PSG Visit. The EoT PSG is conducted similarly to the Baseline PSG.

A subset of up to 12 participants in the narcolepsy cohort who complete the EoT Visit 4 PSG will return to the study site for 1 additional overnight PK Visit (Visit 4a) while still taking their stable dosage of XYWAV. The PK Visit is recommended to occur the night after the PSG Visit but may occur up to 7 days after the EoT Visit 4 PSG.

[REDACTED]

4. Early Discontinuation Visit

Participants who choose to discontinue study intervention with XYWAV or withdraw early from the study will complete an Early Discontinuation Visit (scheduled as soon as possible after the participant discontinues XYWAV treatment [see Section 7.2]). For PSG data to be

collected, participants must have titrated XYWAV and completed at least 1 week of the SDP; for discontinuation or withdrawal prior to this, PSG and the pre-PSG questionnaire will not be completed. Participants will be asked to complete other assessments if they are willing. These participants will also complete a Safety Follow-up Visit approximately 2 weeks after their last dose of XYWAV study intervention.

5. Safety Follow-up Period (2 weeks)

Participants will complete a Safety Follow-up Visit approximately 2 weeks after taking their last dose of XYWAV. Participants will not be monitored beyond the Safety Follow-up Visit.

4.2. Scientific Rationale for Study Design

The purpose of this study is to contribute additional medical and scientific information relative to XYWAV treatment for IH and narcolepsy. XYWAV, a medication that is taken at night, is efficacious in reducing daytime symptoms of narcolepsy and IH. The relationship between sleep effects and daytime symptoms with XYWAV treatment is of strong medical and scientific interest. No studies of sleep effects of XYWAV have been performed in IH or narcolepsy.

In narcolepsy, clear pathology of sleep is seen. Studies consistently characterize sleep as disrupted (fragmented), with reports of frequent brief nightly awakenings and associated reports of poor sleep quality. Polysomnographic studies consistently show frequent awakenings and/or arousals (briefer awakenings) after sleep onset, more N1 (light) sleep, and more frequent shifts to N1 or wake from deeper stages of sleep (Roth, 2013). The consensus of the International Experts' Panel on Narcolepsy was that DNS can be distressing for patients with narcolepsy and that management of DNS warrants consideration (Roth, 2013). There remains a lack of clarity regarding the definition of DNS, as many sleep-related symptoms and conditions disrupt sleep quality in narcolepsy; however, the consistent intrinsic sleep instability that results in frequent spontaneous awakenings and sleep stage transitions is thought to be major contributor to DNS (Maski, 2022).

In 2 clinical Phase 3 studies of XYREM treatment in narcolepsy, the sleep effect observed was a dose-related significant increase in the duration of slow wave sleep (N3), with increased depth of sleep (assessed as delta power) and significantly decreased N1 sleep, REM sleep, and number of awakenings after 8 weeks of treatment; the changes in nocturnal sleep coincided with significant decreases in the severity and frequency of daytime symptoms (Black, 2010). Similar effects were observed in a study of participants with narcolepsy taking modafinil (Black, 2009). In post-hoc analyses, XYREM treatment significantly reduced stage shifts from deeper to lighter stages of sleep, ie, from N2/N3/REM to Stage N1/Wake, Stage N2/N3 to Stage N1/Wake, and from REM to Stage N1/Wake (Roth, 2017; Dauvilliers, 2017). Similar analyses will be performed to establish XYWAV's efficacy on improving sleep fragmentation and increasing sleep stability in participants with narcolepsy. In addition, the study will include participants with NT1 or NT2, allowing for characterization of phenotype differences. It is expected that XYWAV will have similar treatment effects on sleep architecture and reduction of sleep fragmentation. Although the effects of a high-sodium bedtime load on sleep architecture is unknown, the lower sodium content in XYWAV may have additional benefits.

[REDACTED]

[REDACTED]

4.2.1. Patient Input Into Design

A Patient Advisory Board, including patients with IH or narcolepsy, was held to obtain input into this study, and patient feedback was incorporated into the protocol. Key feedback was obtained regarding sponsor-provided assistance to participants undergoing washout of oxybate medication, duration of the SDP, time window for the optional PK Visit 4a, improved participant comfort when completing the Visit 2 and Visit 4 assessment batteries, relevance of the study assessments, and reporting of individual participant data to a participant after the conclusion of the study.

4.3. Justification for Dose

For the main portion of this study, the XYWAV dose range is consistent with the recommended dosage range for XYWAV in adult patients with narcolepsy or IH, ie, 6 to 9 grams nightly (XYWAV USPI; XYWAV PM).

[REDACTED]

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

Participants are considered to have completed the study if they have completed all phases of the study, including the last scheduled procedure shown in the SoA in Section 1.3.

cohorts in this study:

Narcolepsy Cohort: Baseline assessments are with the participant off oxybate treatment; participants may titrate XYWAV up to 9 grams nightly and a subset of participants will complete optional PK assessments at EoT (V4a).

[illegible]

Participants are eligible to be included in the study only if all the following criteria apply:

1. Is 18 to 75 years of age (inclusive) at the time of signing the ICF.

2. Has a primary diagnosis of IH meeting ICSD-3 criteria or narcolepsy (Type 1 or Type 2) meeting ICSD-3 or DSM-V criteria.

3. If not currently taking oxybate medication, has clinically significant symptoms of EDS with an ESS score > 10 at Screening Visit 1. If currently taking oxybate medication, has an ESS score > 10 at the Baseline Visit 2 PSG (after Washout Period).
[REDACTED]
[REDACTED]
4. If currently treated with antiepileptics and/or alerting agents, has been taking the same dosage for at least 1 month prior to Screening Visit 1 and has no current plans to adjust the dosage during the study period. NOTE: Alerting agents refer to either traditional stimulants (eg, amphetamines, methylphenidates) or wake-promoting agents (eg, modafinil, pitolisant, solriamfetol).
5. If currently treated with nicotine replacement therapy, has been taking the same dosage for at least 1 month prior to Screening Visit 1 and has no current plans to adjust the dosage during the study period.

Sex and Contraceptive/Barrier Requirements

6. Participant is male or female.
NOTE: Specific criteria for female participants are listed below; criteria for male participants may be found in [Appendix 4](#).
 - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
 - Is a woman of nonchildbearing potential
 - OR
 - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in [Appendix 4](#), during the study intervention period and for at least 7 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
 - A WOCBP must have a negative highly sensitive (serum) pregnancy test result as required by local regulations during screening (see Section [8.3.8](#)).
 - Additional requirements for pregnancy testing during and after study intervention are provided in Section [8.3.8](#).

The investigator is responsible for review of medical history, contraception history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an undetected early pregnancy.

Informed Consent

7. Is willing and able to provide informed consent, as described in Section [10.1.3](#), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other

8. Is willing and possesses the ability to comply with study design schedule and other study requirements (eg, completing PSG as specified, wearing actigraphy device on wrist, completing assessments as specified, complying with study dosing instructions).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Shows evidence of a previous untreated or inadequately treated sleep disorder considered by the investigator to negatively impact the conduct of the study, including sleep-disordered breathing, parasomnias, circadian rhythm sleep disorders, or restless legs syndrome determined by a previous sleep-laboratory diagnosis or interview utilizing modules of the Diagnostic Interview for Sleep Patterns and Disorders.
2. Shows evidence of untreated or inadequately treated sleep-disordered breathing during Baseline Visit 2 PSG defined as an AHI > 10, using the US CMS rules ([CMS.gov](https://www.cms.gov)).
3. Has succinic semi-aldehyde dehydrogenase deficiency by medical history.
4. Has uncontrolled hypothyroidism as determined by central clinical laboratory test results, with investigator discretion.
5. Has a current seizure disorder.
6. Has a history of head trauma associated with loss of consciousness in the past 5 years or if an event occurred more than 5 years prior to screening, experiences sequelae due to the event.
7. Has a history or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-V criteria.
8. Has a history or presence of any unstable or clinically significant medical condition (eg, chronic pain condition that may impact sleep), behavioral or psychiatric disorder (including active suicidal ideation or current or past [within 1 year] major depressive episode), or history or presence of another neurologic disorder or surgical history that

might affect the participant's safety and/or interfere with the conduct of the study, in the opinion of the investigator.

9. Has any other significant disease or disorder that, in the opinion of the investigator, may either put the participant, other participants, or study staff at risk because of participation in the study, may influence the result of the study, or may affect the participant's safety or ability to take part in the study.
10. Has recently taken (ie, within 1 month prior to screening), is taking, or plans to take any of the following:
 - a. A substance or medication contraindicated with XYWAV use, specifically alcohol and sedative hypnotics (ie, benzodiazepines, barbiturates, non-benzodiazepine hypnotics)
 - b. A medication with a known drug-drug interaction with XYWAV (ie, valproic acid or divalproex sodium)
 - c. A medication that may have similar EEG effects to XYWAV (ie, baclofen, gabapentin, pregabalin, tiagabine)
 - d. Medications known to have clinically significant CNS sedating effects:
 - Dual orexin receptor antagonists (ie, suvorexant, lemborexant, daridorexant)
 - Melatonin receptor agonists (ie, ramelteon, tasimelteon)
 - Antipsychotics
 - Anti-epileptics or antidepressants with known substantial sedation profiles (except when used as an anticonvulsant agent)
 - Opioid analgesics
 - General anesthetics
 - e. Other medications, natural health products, or substances from which the participant experiences clinically significant sedation (eg, sedating antihistamines or natural sleep aids).

For the duration of the study, participants must abstain from these medications/substances or any other medication from which the participant experiences sedation in the opinion of the investigator. Treatment must have been discontinued for at least 2 weeks or 5 half-lives prior to enrollment (whichever is longer).

The investigator may use clinical judgement in allowing the continuation of medications that are not otherwise excluded and that may have CNS sedating effects, provided that the participant has been on a stable dose (ie, at least 1 month with no current plans to adjust the dose).

A comprehensive list of prohibited medications is provided in the Investigator Trial Site File.

11. Has nicotine-use disorder that impacts sleep (ie, a participant who routinely wakes during the night to smoke).
12. Has excessive caffeine consumption that may impact sleep (ie, participant routinely consumes >10 caffeinated beverages per day [1000 mg/day caffeine]).
13. Is currently prescribed a dosage of oxybate exceeding a dosage of 9 grams nightly or any single dose more than 6 grams.

Prior/Concomitant Therapy

14. Is unwilling to complete a Washout Period (for current oxybate users only [REDACTED]).

Prior/Concurrent Clinical Study Experience

15. Has received any other investigational drug within 30 days or 5 half-lives (whichever is longer) prior to screening or plans to use an investigational drug (other than the study intervention) during the study. Note: those who have completed participation in a different XYWAV study may enroll directly into Study JZP258-407 without waiting 30 days from the last dose of study intervention in the prior study.

Diagnostic Assessments

16. Has a laboratory test value (clinical chemistry) outside the laboratory reference range that is considered to be clinically significant by the investigator. NOTE: Screening laboratory tests may be repeated once during the Screening Period.

Other Exclusions

17. Has an occupation that requires nighttime or variable shift work.
18. Has plans for travel across more than 3 time zones during the study.
19. Was previously eligible for this study but discontinued study intervention or was withdrawn early.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.3. Lifestyle Considerations

Lifestyle considerations for this study are specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2).

Participants will be advised to take XYWAV at least 2 hours after eating (as directed in the XYWAV USPI and PM).

Participants will be counseled about maintaining habitual bedtimes, travel, and excessive caffeine intake. Caffeine cannot be consumed during the morning test battery that occurs following the Baseline PSG or the EoT PSG (refer to Section 8.1.7).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. Screen failures include participants who are ineligible (ie, those who do not meet inclusion/exclusion criteria) and participants who withdraw consent for any reason prior to receiving study intervention.

A minimal set of screen-failure information is required to ensure transparent reporting of screen failures, to meet the CONSORT publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once following approval and appropriate documentation by the study medical monitor. Rescreening may occur following the resolution of transient exclusionary conditions, stabilization of conditions that were exclusionary when unstable (eg, electrolyte abnormalities), or after reaching a stable period (at least 1 month) after a change in medication and/or regimen. Individuals who are approved for rescreening must be reconsented and repeat all screening procedures. This includes the assignment of a new participant number.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study.

6.1. Study Intervention(s)/Treatment(s) Administered

Table 6: Study Treatment/Intervention

Treatment Arm	Intervention /Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Packaging	Label	Storage Conditions
1	JZP258 (XYWAV)	Solution	0.5 g/mL mixture of calcium, potassium, magnesium, and sodium oxybates (0.413 g/mL oxybate)	<p>XYWAV will be titrated to an optimal dosage for each participant based on efficacy and tolerability with guidance from the investigator.</p> <p>Narcolepsy Cohort: XYWAV USPI and PM recommended effective dosage range is 6 to 9 grams/night divided (equally or unequally) into 2 doses, with the first dose taken at bedtime and the second taken 2.5 to 4 hours later.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>IH Cohort: XYWAV dosage is once or twice nightly. Participants taking a once-nightly regimen may take up to 6 grams/night as a single dose. Participants taking a twice-nightly regimen may take up to 9 grams/night as 2 divided doses.</p>	Oral	Experimental	Provided centrally by the sponsor	<p>Study intervention will be provided in bottles with inserted Press-In Bottle Adapter (and accessories, eg, dosing cups and dosing syringe), labeled according to country-specific guidelines.</p> <p>All packaging and label operations are according to current Good Manufacturing Practices and local requirements and regulations.</p> <p>Child-resistant packaging is as required.</p>	Open label	Store at room temperature between 20°C and 25°C (excursions permitted between 15°C and 30°C).

Abbreviations: IH = idiopathic hypersomnia; PM = Canadian Product Monograph; USPI = United States Prescribing Information.

NOTE: The Intervention Period begins on the day that participants are instructed to take their first dose during the Titration Period after their eligibility has been confirmed following the Baseline Polysomnography Visit. Participants will be provided detailed instructions regarding their treatment regimen during the Intervention Period (see Section 4.1).

6.2. Preparation/Handling/Storage/Accountability

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study intervention (XYWAV) in accordance with the study protocol and any applicable laws and regulations.

For this study, XYWAV preparation, handling, and storage are performed according to the USPI and PM.

- Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual located in the Investigator Site File.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized study staff may supply or administer study intervention.
- The investigator must have country-appropriate controlled substance licensing (eg, Drug Enforcement Administration license for Schedule III drugs, applicable to US study sites) and ensure storage per local regulations or requirements.
- All clinical study materials will be labeled according to specific country requirements.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator, institution, or head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Assignment to Study Intervention

Enrolled participants are assigned to treatment with XYWAV, the only study intervention in this study.

A participant is considered enrolled in the study by providing informed consent to participate in the study.

All participants who sign the 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 cannot be reassigned to another study participant once assigned.

After a participant number is assigned, the participant will enter the Screening Period and, subsequently, the Baseline Period (if the participant continues to meet eligibility criteria). Participants who meet all eligibility criteria at the conclusion of the Baseline Period will enter

the study and continue to the Intervention Period. As this is a single-arm open-label study, all participants will receive XYWAV during the Intervention Period.

6.4. Blinding/Masking

This is an open-label study with no blinding.

6.5. Study Intervention/Treatment Compliance

Jazz Pharmaceuticals (sponsor) will provide open-label bottles of XYWAV oral solution 0.5 g/mL for the study (study intervention). Participants will be instructed to keep all bottles (including empty bottles) for compliance measurements.

The participant will self-administer XYWAV as directed by study personnel and follow dosing guidance provided in the USPI and PM (XYWAV USPI; XYWAV PM), including taking the first nighttime dose of XYWAV at least 2 hours after the last meal. The participant will complete an electronic study intervention dosing diary (Participant Dosing eDiary) daily starting at the SDP through the EoT Period. Completeness of the XYWAV dosing diary will be discussed and assessed at each visit. Study personnel will counsel participants who have not been compliant with dosing and eDiary completion.

Treatment compliance will be measured by study personnel and recorded on the participant's drug accountability log. A designated study staff member will count and record the number of bottles of study intervention (XYWAV) dispensed and returned. The volume of solution dispensed and returned will also be recorded.

A record of the quantity of XYWAV dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, dosage information, dose and regimen adjustments, and any deviation(s) from the prescribed treatment regimen or dosage (including overdosing, described in Section 6.8) should be recorded as applicable.

Suspected misuse or potential abuse of XYWAV should be investigated, and the participant should be counseled when there is a discrepancy between the returned volume compared with the expected returned volume.

Study sites are responsible for identification and documentation of missing bottles during the study. Unused study intervention (partially used, unused, or empty bottles) will be returned to the study site per sponsor instructions. Any unreturned bottles must be requested through the end of study, and if not returned to the study site or designee, the reason must be documented. If not returned at the final visit, the site must document 3 attempts (whenever possible, 2 telephone calls and a certified letter to the participant) for bottles to be returned after the participant's completion of the study.

6.6. Dose Modification

Once XYWAV dosage is stable via titration for each participant, dose modification (ie, decrease in dose or dose interruption) is permitted in the case of an AE, at the discretion of the investigator. The study medical monitor should be informed of any XYWAV dosage changes or interruptions after the SDP has started and all dose modifications will be recorded.

6.7. Continued Access to Study Intervention After the End of the Study

Following completion of this study, participants may be treated with XYWAV outside of this study (in countries where XYWAV has been approved) or another standard of care according to physician discretion.

6.8. Treatment of Overdose, Medication Errors, or Misuse

Overdose (defined as any dose administered or received that is higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study intervention), and misuse of the study intervention are considered OREs. The method for completing and transmitting reports of these experiences is provided in [Appendix 3](#).

If any overdose, medication error, or misuse of the study intervention results in an AE, this must be recorded. If the AE is serious, it must also be reported as described in [Appendix 3](#).

Decisions regarding dose interruptions or modifications will be made by the investigator, in consultation with the medical monitor, based on the clinical evaluation of the participant.

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until XYWAV can no longer be detected systemically (at least 24 hours postdose).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The study medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants treated with anticonvulsants and/or alerting agents or nicotine-replacement therapy must have been taking the same dosage regimen for at least 1 month prior to screening and must agree to take the same dosage throughout the study. Refer to the inclusion and exclusion criteria for details (see Section [5.1](#) and Section [5.2](#)). A comprehensive list of prohibited medications is provided in the Investigator Trial Site File.

Use of concomitant alerting agents, and/or non-oxybate antiepileptic medications will be allowed at a stable dosage and monitored throughout the study duration.

At the end of Visit 1, participants who are currently taking oxybate (eg, XYWAV or XYREM, or other oxybate medication) and who are still considered eligible will discontinue their oxybate medication for 2 weeks (ie, washout) before baseline assessments can begin [REDACTED]

[REDACTED]. NOTE:

Medication washout is not applicable to eligible participants who are oxybate naïve or participants who have previously taken oxybate but have not taken oxybate medication within the past 2 weeks. Discontinuation of other antiepileptics and/or alerting agents is not necessary during washout, but the dosage must remain stable throughout the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may discontinue from study intervention at any time for any reason or at the discretion of the investigator. In addition, a participant may be withdrawn from study intervention by the investigator or sponsor for safety, behavioral, compliance, and/or administrative reasons. For participants who discontinue study intervention, all effort should be made to complete the procedures listed in the ED Visit in the SoA in Section 1.3. Participants will be asked to complete the Safety Follow-up Visit 14 days after the last dose of study intervention.

7.1. Permanent Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if possible, remain in the study to capture assessments whenever possible. For PSG data to be captured, participants must have titrated XYWAV and completed at least 1 week of the SDP. For discontinuation prior to this milestone, PSG and the pre-PSG questionnaire will not be completed. The SoA in Section 1.3 details the data to be collected at the time of discontinuation of study intervention (ED Visit) and the Safety Follow-up Visit and provides information on any further evaluations that need to be completed.

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legal representative requests to discontinue study intervention.
- The participant develops an AE or other safety or clinical concern that may compromise the participant's continued participation.
- The participant has a positive pregnancy test result (see Section 8.4.5).
- The participant is noncompliant with study intervention or procedures.
- The sponsor terminates the study prior to completion.
- The investigator determines that the participant should not continue study intervention.
- The participant enrolls in a different clinical study that involves investigational treatment.

Discontinuation of specific study sites, or of the study as a whole, is handled as part of [Study and Site Start and Closure](#) (see Section 10.1.9).

7.2. Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at their own request for any reason (or without providing a reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The SoA in Section 1.3 and Section 4.1 provides details regarding data to be collected at the time of early discontinuation from the study (ED Visit) and the Safety Follow-up Visit. For PSG data to be captured, participants must have titrated XYWAV and completed at least 1 week of the SDP. For discontinuation or withdrawal prior to this milestone, PSG and the pre-PSG questionnaire will not be completed. Participants will be asked to complete other assessments if they are willing.

After discontinuing study intervention, investigators should determine the appropriate care path forward for participants. It is understood and expected that participants will resume their standard of care treatment (potentially including commercially prescribed XYWAV or XYREM).

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to attend scheduled visits and is unable to be contacted by the staff.

The following actions must be taken if a participant fails to attend a required study visit:

- The staff must attempt to contact the participant, reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (whenever possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- If the participant continues to be unreachable, they will be considered to have withdrawn from the study and be lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Information relevant to study assessments and procedures is provided below:

- Study procedures and their timing are summarized in the SoA in Section 1.3.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Some assessments will occur as telephone or telemedicine visits (according to preference of the investigator) as specified in the SoA.
- All screening evaluations must be completed and reviewed by authorized study staff to confirm that potential participants meet all eligibility criteria. The investigator should maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided that the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions will be provided to participants at each visit on relevant aspects of the study.
- Unscheduled visits may be needed (eg, for additional dispensing of XYWAV or any other reason at the investigator's discretion).
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, according to local health authority/ethics requirements.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or qualified designee (consistent with local requirements) must obtain documented consent from each potential participant/legal representative prior to participation in this study. A signed copy of the ICF should be given to the participant, and the original should be placed in the participant's medical records.

8.1.2. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the investigator to ensure that the participant qualifies for the study. Data relative to inclusion/exclusion review will be documented and included in source information for each participant.

8.1.3. Assignment of Participant Number

Each participant who signs the ICF will be considered enrolled and assigned a unique number that will identify the participant throughout the study. Once a number has been assigned, it

cannot be reassigned to another study participant. [REDACTED]
[REDACTED]

8.1.4. Medical History

A 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.

8.1.5. Medication Review (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.

8.1.6. Timing of Study Intervention Dosing

XYWAV should be administered at least 2 hours after a meal. Participants should take each dose of XYWAV while in bed, lie down immediately after dosing, and remain in bed following administration of each dose.

Timing of treatment with XYWAV is according to the XYWAV USPI and PM, with the second dose taken 2.5 to 4 hours after the first dose. [REDACTED]
[REDACTED]

8.1.7. Participant/Site Check-In

During the Screening Period, participants will be educated about the study and procedures and trained on devices, (actigraphy, eDiary). Participants will be asked about habitual sleep/wake schedules and will be advised to avoid excessive travel and maintain consistent bedtimes and avoid excessive caffeine consumption during the study (Section 5.3). Visits may be scheduled in advance as needed (eg, to reserve overnight visit dates, aid with staff scheduling, or based on the participant's schedule).

Throughout the study, study personnel will provide instructions and reminders to participants on items such as completion of the electronic diaries, wearing the actigraphy device, how to complete certain assessments at a PSG Visit, titration, and dosing administration. Study personnel will also advise participants to keep the Baseline and EOT Visits as similar as possible by maintaining similar bedtimes and dinner times. Participants will also be asked to avoid caffeine and napping in the afternoon and evening (after 3pm) prior to and during these visits. These will be opportunities for the site to ensure that participants understand what is expected of them and offer any support needed.

In addition, for those participants undergoing the oxybate Washout Period (ie, participants enrolling in the narcolepsy or IH cohorts who are taking an oxybate treatment at study entry), study personnel should have a discussion with their participants to determine if any sponsor-supported assistance will be needed (eg, transportation, daily check-in telemedicine/telephone calls). This conversation should be initiated at Screening Visit 1 and should be continued throughout the Washout Period to support the participant. These check-ins between study personnel and participants may occur either by telemedicine or by telephone. Note that these participants will be off of oxybate treatment for a total of approximately 3 weeks

(participants will undergo a 2-week Washout Period before proceeding to the Baseline Period and remain off oxybate treatment while completing baseline assessments [refer to [Table 3](#)]).

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA in Section [1.3](#).

8.2.1. Actigraphy

Actigraphy is a noninvasive tool to objectively measure activity profiles and is used to estimate sleep patterns based on validated algorithms. Actigraphy data will be recorded with a wrist-worn device that records movement (3-axis accelerometer), light, and temperature. Participants will be instructed to wear the actigraphy device on the wrist of their nondominant hand. Data outputs include TST and other measures related to sleep and daytime activity patterns.

Participants will be provided with an actigraphy device and instructed on its use (continuous use through indicated visits until the morning following the PSG recording). Participants will be reminded when to start wearing the actigraphy device. At least 7 days of wear are required during the 8-day assessment periods prior to the Baseline and EoT PSG Visits. Participants will be asked to wear the actigraphy device during the Baseline Assessment Period through Visit 2, and from the SDP through Visit 4. [REDACTED]

[REDACTED]

Study staff will be asked to collect and dispense the actigraphy device as specified in the SoA (Section [1.3](#)). Note that participants should be given a newly initiated and charged actigraphy device on Baseline and EoT PSG nights (before the PSG is administered). [REDACTED]

[REDACTED]

[REDACTED]

8.2.2. Sleep Diary

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

Participants will complete the Sleep eDiary daily during the Baseline and EoT Assessment Periods, including during the PSG Visits. The eDiary applications will be deployed on their personal device or a device provided by a central vendor. Participants will be reminded when to start completing the eDiary. At least 7 days of data are required during the 8-day assessment periods prior to the PSG Visits.

8.2.3. Cataplexy Diary (Narcolepsy Type 1 Only)

The change in the weekly rate of cataplexy attacks will be assessed for participants with NT1 using a cataplexy frequency diary. This electronic diary will include a definition of a cataplexy attack (eg, "cause you to actually fall down or you would have fallen if you did not support yourself or make part of your body feel weak"). Each night prior to bedtime, participants will record the number of daily cataplexy attacks experienced in an electronic cataplexy frequency diary (participants should record "0" if no attacks occurred).

Participants will complete the Cataplexy eDiary every day during the Baseline and EoT Assessment Periods, including during the PSG Visits, on their personal device or a device provided by a central vendor. Participants will be reminded when to start completing the eDiary. At least 7 days of data are required during the 8-day assessment periods prior to the PSG Visits.

8.2.4. Study Intervention Dosing Diary

The electronic Study Intervention Dosing Diary (also referred to herein as the Participant Dosing eDiary) includes questions about the participant's stable XYWAV dosage, including number of doses taken per night, and number of grams taken for each dose. If there were any dosage modifications (eg, skipped second dose), questions will be asked to understand what was changed and why planned/unplanned changes to the dosage regimen occurred.

The diary is to be completed every day from the start of SDP through the EoT Period, including the day of the Visit 4 PSG [REDACTED]. Participants will be reminded when to start completing the eDiary on their personal device or a device provided by a central vendor. At least 7 days of data are required during the 8-day assessment period prior to the Visit 4 PSG.

8.2.5. Clinician-Reported Dosing Form

Investigators will be asked to complete a Clinician-Reported Dosing Form electronic questionnaire to capture the details of the treatment regimen for each titration step and reasons for changes, to better understand clinician dosage rationale and confirm the participant's optimized dosage. The form includes questions about the dose amount and regimen at the initiation of titration and collects any changes in administration (amount or regimen) after the weekly Titration Check-in with the participant during the Titration Period. The form will capture the clinician's rationale for dosage changes. Investigators will be provided titration guidelines as follows:

- Participants in the IH and narcolepsy cohorts who enter the study taking oxybate medication (eg, XYWAV, XYREM, or another oxybate medication), after completing the Washout Period and Baseline Visit 2 PSG, will enter the Titration Period with XYWAV titrated to their original dosage (ie, before washout) over a minimum of 2 weeks. Investigators may take up to 6 additional weeks to further optimize the participant's dosage based on clinical judgment.
- XYWAV will be titrated for participants who are naïve to oxybate medication to an optimal dosage over a period of up to 8 weeks based on the investigator's clinical judgment.

[REDACTED]

8.2.6. Epworth Sleepiness Scale

The ESS is a self-administered questionnaire with 8 items (Johns, 1991; Johns, 1992). Respondents rate on a 4-point scale (0 to 3) their usual chances of dozing off or falling asleep while engaged in 8 different activities. Most people engage in those activities at least occasionally, although not necessarily every day. Responses range from 0 (would never doze) to 3 (high chance of dozing). The ESS total score (the sum of 8 item scores, each 0 to 3) can range from 0 to 24. Higher ESS total scores are associated with higher sleep propensity in daily life, also referred to as “daytime sleepiness.” The ESS has been validated in several conditions, including narcolepsy (Johns, 1994).

8.2.7. Idiopathic Hypersomnia Severity Scale (Idiopathic Hypersomnia Cohort Only)

The IHSS (Dauvilliers, 2019) is a 14-item self-reported instrument that assesses the severity and functional consequences of IH symptoms. Questions capture symptoms of excessive sleepiness, sleep inertia, and long sleep duration. IHSS total scores range from 0 to 50.

8.2.8. Narcolepsy Severity Scale (Narcolepsy Cohort Only)

The NSS (Dauvilliers, 2020) is a 15-item self-administered questionnaire (score: 0 to 57) that assesses the severity and consequences of the 5 major narcolepsy symptoms such as daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and DNS. A modified version omitting the questions about cataplexy will be used for participants with NT2.

8.2.9. Patient Global Impression of Severity

The self-administered PGI-S is a single-item, 7-point, Likert-type scale that is widely used in clinical studies to assess the severity of a condition. Using this scale, participants will be asked to rate the level of severity of each of the following: sleep inertia, fatigue, and overall symptoms. Response options include: 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe.

8.2.10. Patient Global Impression of Change

The self-administered PGI-C is a 7-point Likert-type scale that is widely used to evaluate efficacy in a clinical study by assessing a participant’s impression of response to treatment. Using this scale, participants will be asked to rate their impression of change for each of the following: sleep inertia, fatigue, and overall symptoms. Response options include 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

8.2.11. British Columbia Cognitive Complaints Inventory

The BC-CCI was developed to measure cognitive complaints in individuals with major depressive disorder (Iverson, 2013). It is a 6-item self-report measure that asks respondents to rate problems with specific cognitive symptoms using a 4-point scale (0 “Not at all” to 3 “Very much”). The total score ranges from 0 to 18 from assessment of domains of memory, concentration, trouble expressing thoughts, word-finding, and problem solving. Higher scores indicate greater severity of cognitive impairment. Three additional items that ask about how

these symptoms impact work, relationships, and social/recreational activities are also included to provide further information on the nature of functional impairment.

8.2.12. Orthostatic Hypotension Questionnaire

The OHQ is a validated 10-item self-administered questionnaire (Kaufmann, 2012). The OHQ consists of 2 components: the Orthostatic Hypotension Symptom Assessment, to measure the presence and severity of symptoms, and the Orthostatic Hypotension Daily Activity Scale, to measure the impact of orthostatic symptoms on daily activities.

8.2.13. Pre-Polysomnography Questionnaire

The self-administered pre-PSG questionnaire, administered the night of PSG, includes questions about activities during that day (eg, naps, any unusual events, caffeinated beverages) that may impact the PSG.

8.2.14. Polysomnography

Each participant's sleep architecture will be characterized by PSG during overnight study visits, as specified in the SoA in Section 1.3. Participants should be reminded to bring any treatment/therapy that they typically use at night (eg, continuous positive airway pressure machine, oral device, or medication) to the clinic for PSG study overnight visits. Titration studies will not be performed. The Baseline PSG Visit may be scheduled ahead of time, after most of the eligibility criteria have been met during the Screening Period, with the understanding that screening laboratory assessments and results from the Baseline PSG must be confirmed prior to beginning the Intervention Period.

Participants will undergo a nocturnal PSG using an ad lib protocol to allow sufficient time in bed with a natural awakening time; PSGs should be scheduled to allow a minimum of 10 hours in bed, unless the participant awakens naturally earlier. Bedtime will be determined by identifying the habitual bedtime. The same bedtime will be used for Baseline and EoT PSG Visits. The latest wake-up time should be around noon (for logistic reasons); however, participants should not be awakened from non-REM stage-3 sleep.

The PSG recordings will be obtained according to a standard protocol (with a standardized montage), procedures for biocalibrations and technician notations, and technical specifications as outlined in the study PSG Manual, which will be provided to each study site. Participants will have electrodes and sensors applied, which is estimated to take up to 1 hour for a standard hook-up. The PSG recordings must be immediately reviewed by the site staff the morning after the PSG to confirm eligibility and validity before dispensing study intervention (XYWAV). In the event that a PSG is invalid (eg, < 6 hours recorded due to technical, environmental, or other factors), a repeat PSG should be scheduled as soon as possible. All assessments associated with the PSG Visit will also be repeated at this second PSG.

After participant eligibility has been confirmed by site staff at the end of the Baseline PSG (including a review of the AHI during the Baseline PSG [see exclusion criterion 2]), study intervention will be dispensed to the participant. Study personnel should send the PSG recording to the central PSG vendor within 24 hours of completion of the visit. Details, including data transfer methods and required personnel, will be provided in the PSG Manual. [REDACTED]

[REDACTED]

For participants undergoing PK evaluations, it should be noted that the PK Visit cannot be completed during the same study visit as the PSG Visit. The PK Visit is recommended to occur the night after the PSG Visit, but can occur up to 7 days after the PSG Visit.

For PSG data to be captured, participants must have titrated XYWAV and completed at least 1 week of the Stable Dose Period.

8.2.15. Karolinska Sleepiness Scale

The KSS is a single-item self-administered scale that measures subjective level of sleepiness at a particular time during the day. It is a 9-point scale from “extremely alert” to “extremely sleepy, can’t keep awake.” Scores on the KSS increase with longer periods of wakefulness and strongly correlate with the time of the day. On this scale, participants indicate which level best reflects the psycho-physical state experienced in the last 10 minutes. The KSS is a measure of situational sleepiness. It is sensitive to fluctuations ([Shahid, 2012](#)). The KSS will be administered within approximately 2 minutes of the participant’s natural awakening time and immediately before and after each of the PVT tests.

8.2.16. Psychomotor Vigilance Test

The PVT is a test used to measure reaction time, alertness, and the impacts of sleep inertia. The PVT is administered in the morning immediately following the completion of PSG [REDACTED]. It will be administered in relation to the participant’s natural awakening time at ~ 10 minutes after awakening, and again at ~ 40 and ~ 90 minutes after awakening. Each PVT test is 10 minutes in duration. During the PVT, participants are instructed to respond to a stimulus presented at random intervals for the 10-minute duration. Participants are instructed to respond to the appearance of the stimulus as quickly as they can while trying to avoid false starts ([Dinges, 1985](#)).

A PVT training session will be conducted in the evening prior to the PSG. Upon awakening the morning after the PSG, participants will complete the KSS (see Section 8.2.15) before taking a restroom break. Some PSG sensors will continue recording during the PVT assessments. Within 10 minutes after awakening, the participants will initiate the test battery consisting of a computerized version of the PVT with the KSS administered immediately before and after each PVT. This test battery will be administered in total 3 times before the completion of the visit. Participants will also have specific times to complete remaining baseline assessments between trials.

8.2.17. Functional Outcomes of Sleep Questionnaire-10

The FOSQ-10 ([Chasens, 2009](#)) is a self-administered questionnaire designed to assess the impact of daytime sleepiness on activities of daily living. It consists of 10 items measuring the participant’s general productivity, activity level, vigilance, and intimacy and sexual relationships. For each item, participants are asked to rate the level of difficulty in completing an activity on a 4-point Likert scale (from 1 “Yes, extreme” to 4 “No”). From the FOSQ-10 a total score is calculated: a higher score indicates better functional status. The FOSQ-10 is a reduced version of

the original FOSQ-30 ([Weaver, 1997](#)). The FOSQ-10 was tested and found to be a psychometrically strong instrument that performed similarly to the long version.

8.2.18. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The self-administered WPAI:SHP is a 6-item questionnaire that measures work time missed and work and activity impairment because of a specified health problem. When administering the WPAI:SHP, participants will be instructed to consider “IH” as the specified health problem for the IH cohort and “narcolepsy” as the specified health problem for the narcolepsy cohort. The validity of the WPAI has been established in several disorders ([Reilly, 1993](#)).

8.2.19. Patient Health Questionnaire-9

The PHQ-9 is a 9-item scale of depressive symptoms developed based on the 9 diagnostic criteria for major depressive disorder in the DSM-IV. It is validated and documented in a variety of populations ([Kroenke, 2001](#)).

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA in Section [1.3](#).

[REDACTED]

8.3.1. Physical Examinations

Physical examinations will be performed as described below:

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any abnormalities identified during the screening PE should be recorded as medical history.

- Height and weight will be measured and recorded at the Screening Visit (used to calculate BMI).
- Weight will be measured and recorded at other times as indicated in the SoA in Section 1.3.

8.3.2. Vital Signs

Vital signs will be measured as follows:

- Body temperature, heart rate, respiration rate, and blood pressure will be assessed at the Screening Visit, PSG Visits, and the PK Visits. [REDACTED]
- Measuring BP and heart rate should be preceded by at least 5 minutes of rest and obtained while the participant is seated in a quiet setting without distractions (eg, television, cell phones).
- The BP and heart rate measurements (to be taken before blood collection for laboratory tests) will consist of 3 consecutive BP and HR measurements recorded at intervals of at least 1 minute. This should be measured with a completely automated device. The average of the 3 BP and heart rate readings will be recorded (calculated separately for SBP and DBP).
- Clinically significant abnormal vital sign results should be documented by the study site in the medical history (at screening) or as AEs (after initiating study intervention).

8.3.3. Apnea/Hypopnea Index

An AHI is a derived variable from the PSG montage, and it will be measured at the PSG visits as outlined in the PSG Manual. An AHI is the number of apneas and hypopneas recorded during the PSG per hour of sleep. It is expressed as the number of events per hour ([CMS.gov](https://www.cms.gov)):

- Apnea is defined as cessation of breathing for at least 10 seconds.
- Hypopnea is defined as a reduction of ventilation of at least 30% for at least 10 seconds that results in a decrease in arterial oxygen saturation of at least 4%.

8.3.4. Pulse Oximetry

Pulse oximetry for the PK Visits will be performed as follows:

- SpO₂ will be monitored continuously by pulse oximetry from immediately before the first dose through 8 hours after the first dose.
- Measurements should be taken and recorded as noted in the SoA in Section 1.3 (prior to PK blood collection).
- An additional measurement should be taken while the participant is awake before release from the study site.

Pulse oximetry is standard for a PSG montage, and it will be measured at the PSG Visits as outlined in the PSG Manual.

8.3.5. Electrocardiography

Electrocardiography will be performed as follows:

- During the Screening Visit (Visit 1), a single 12-lead ECG will be obtained as outlined in the SoA in Section 1.3.
- For the optional PK Visit (Visit 4a), ECG will be obtained prior to discharge.

8.3.6. Clinical Safety Laboratory Assessments

Clinical laboratory assessments will be performed as follows:

- [Appendix 2](#) provides the list of clinical laboratory tests to be performed, and the SoA (see Section 1.3) details the timing and frequency.
- The investigator must review the laboratory report and document this review. Laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 24 hours after the last dose of study intervention (and considered by the investigator to be related to study intervention) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor:
 - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor should be notified.
 - All protocol-required laboratory tests, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the SoA (see Section 1.3).
 - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), the results must be recorded.

8.3.7. Alcohol and Drug Screen

Breath alcohol tests and urine drug screening will be performed at the study site as specified in the SoA in Section 1.3. Test results will be recorded, and participants who are noncompliant should be discontinued from the study.

8.3.8. Pregnancy Testing

Pregnancy testing (serum and urine) will be performed as indicated in SoA in Section 1.3.

- Section 5.1 Inclusion Criteria details the pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at certain visits during intervention, as specified in the SoA.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the EoT or ED Visit (as specified in the SoA in Section 1.3).
- Additional serum or urine pregnancy tests may be performed as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during the participation in the study.

8.3.9. Suicidal Ideation and Behavior Risk Monitoring

When informed consent or assent has been given, families and caregivers of participants being treated with XYWAV should be alerted regarding the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

At screening, the Baseline/Screening version of the C-SSRS will be administered to participants to exclude any individuals with active suicidal ideation and/or behavior. The C-SSRS must be administered by a qualified site rater who has received training in its administration. If active suicidal ideation (eg, a positive response to Question 4 or 5 on the C-SSRS) or behavior (eg, a positive response to any suicidal behavior question on the C-SSRS) is noted, a same-day evaluation should be conducted by a trained mental health practitioner, and the sponsor or designee should be contacted to discuss the participant's continuation in the study.

Active suicidal ideation or behavior occurring after the participant has initiated study intervention must be recorded as an SAE and reported to the sponsor or designee within 24 hours of first knowledge of the event by study personnel. The participant should also undergo a risk assessment by a trained mental health practitioner.

All factors contributing to suicidal ideation and/or behavior should be evaluated, and consideration should be given to discontinuation of the study intervention.

8.3.10. Brief Neurologic Examination

Prior to discharge after the PK Visit, investigators or qualified study staff should evaluate participants for alertness and sleepiness before they are discharged. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided in [Appendix 3](#).

The definitions of unsolicited and solicited AEs are provided in [Appendix 3](#).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for monitoring all AEs. This includes events reported by the participant (or by a caregiver, surrogate, or the participant's legally authorized representative, when appropriate).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3](#).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

Adverse medical conditions that are reported after obtaining informed consent but before the start of study intervention will be recorded as medical history/current medical conditions, not as AEs, except in participants who enter the Washout Period; any AEs during washout will be collected as washout-emergent AEs and will not be added to medical history.

All AEs (and SAEs) will be recorded from the start of study intervention until the Safety Follow-up Visit at specified time points (see SoA in Section [1.3](#)) and will be defined as TEAEs.

NOTE: All SAEs that occur after the consent form is signed but before study intervention/treatment must be reported by the investigator if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

If an SAE results in a participant's exclusion from the study, occurs as a result of a protocol-specified intervention, and is ongoing at time of study exclusion, the SAE must be followed per Section [8.4.3](#).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of first knowledge of the event by study personnel, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on new AEs or SAEs occurring after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and they consider the event to be reasonably related to the study intervention or study participation, the investigator should promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up on the status of each AE/SAE with each participant at subsequent visits/contacts and the AE and SAE reports must be updated with any new information obtained at these visits. All nonserious AEs will be monitored until the participant's last study visit. All SAEs, including SAEs that are ongoing at a participant's last study visit, will be monitored until resolution or stabilization, the event is

otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification from the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities regarding the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review, file it along with the IB, and notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The Reference Safety Information for the determination of expectedness of XYWAV can be found in the IB.

8.4.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention until 7 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).
- Although pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be monitored to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor. Neonates will be monitored for 6 months after birth.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. Although the investigator is not obligated to actively seek this

information in former study participants/pregnant female partners, an investigator may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.5. Pharmacokinetics

A subset of up to 12 participants with narcolepsy (stable dosage of ≤ 9 grams nightly) who complete the EoT PSG Visit may choose to return to the study site for an optional overnight PK Visit while still taking their stable dosage of XYWAV. Confirmation of consent should be verified before the participant proceeds to the PK Visit.

[REDACTED]

[REDACTED]

[REDACTED]

Note that PK Visits may not occur during the same study visit as a PSG Visit. The PK Visit is recommended to occur the night after the PSG Visit, but may occur up to 7 days after the PSG Visit.

Whole-blood samples will be collected at prespecified timepoints as outlined in the SoA (see Section 1.3). Actual times of dose administration and blood samples for oxybate concentrations must be precisely recorded on the source document and in the eCRF. Blood samples will be processed to obtain plasma samples, which will be analyzed for oxybate concentrations using a validated bioanalytical method. Separate instructions on sample collection, processing (blood to plasma), storage, and shipping will be provided to the site prior to sample collection.

Participants will discontinue study intervention after completing the PK Visit.

8.6. Pharmacodynamics

Pharmacokinetic/Pharmacodynamic analyses will be conducted and reported separately.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional details will be described in the SAP. Substantial modifications to study endpoints or analytical methods will be justified and documented in the Trial Master File as necessary.

9.1. Statistical Hypotheses

Formal hypothesis testing will be conducted using the Completer Set (defined in Section 9.2) for the following endpoints by cohort (IH and narcolepsy cohorts only):

Narcolepsy Cohort

1. ESS total score (decrease from baseline)
2. Total sleep stage shifts from N1/N2/N3/REM to wake and N2/N3/REM to N1 (decrease from baseline)
3. Duration of N3 sleep (increase from baseline)
4. Total number of nocturnal awakenings (decrease from baseline)

Idiopathic Hypersomnia Cohort

1. ESS total score (decrease from baseline)
2. IHSS total score (decrease from baseline)

Each endpoint will be estimated using a mixed model with repeated measures of the change from baseline at each scheduled follow-up visit, adjusted for the baseline value. The parameter of interest for each endpoint, the least-squares mean difference at the EoT Visit, will be compared against a null hypothesis value of 0.

Multiplicity control will be achieved using a sequential testing strategy conducted separately for each cohort. Listed endpoints will be tested in the order shown above. Hypothesis tests with 2-sided $P < 0.05$ in the expected direction will be considered statistically significant. If any ordered endpoint should fail to reject the null hypothesis, subsequent hypothesis tests will be considered nominal. Hypothesis tests for endpoints not included in the sequential testing procedure will be considered nominal.

9.2. Analysis Sets

Participant Analysis Set	Description
Enrolled Set	All participants who sign the ICF. This analysis set will be used to summarize participant enrollment, disposition, and protocol deviations.
Safety Set	All participants who enroll in the study and take at least 1 dose of XYWAV after the Baseline Period. The safety analysis set will be used to summarize the safety and tolerability endpoints.

Participant Analysis Set	Description
Effectiveness Set	All participants who enroll in the study, take at least 1 dose of XYWAV after the Baseline Period, and complete an EoT Visit (V4 PSG or ED). This analysis set will be used for supplemental analyses of effectiveness endpoints.
Completer Set	All participants who enroll in the study, take at least 1 dose of XYWAV after the Baseline Period, complete the SDP, and complete the V4 PSG EoT Visit. This analysis set will be used for primary analyses of effectiveness endpoints.
PK Analysis Set	All participants with narcolepsy who complete a PK Visit. The PK analysis set will be used to analyze the PK data, including within-visit safety endpoints.

Additional pertinent population sets may be detailed in the study SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

All analyses will be conducted separately for the IH and narcolepsy study populations.

Standard descriptive statistics will be provided for all assessments at all scheduled time points. Descriptive statistics for continuous endpoints will include mean and SD; quartiles (25th, 50th [median], and 75th); and minimum and maximum values. Descriptive statistics for categorical endpoints will include counts and percentages.

Study baseline will be defined as the last measurement observation (scheduled or unscheduled) taken during the study baseline period (at or prior to Visit 2). [REDACTED]

A more technical and detailed description of the statistical analyses will be provided in the SAP.

Raw data will be converted to standardized datasets according to CDISC standards and principles, but CDISC validation will not be required. Unless otherwise specified, data file processing will be performed, and summary outputs will be generated, using SAS version 9.4 (or later).

9.3.2. Endpoints

Estimand components, including summary measures for primary and secondary endpoints, are detailed in Section 3. Alternative estimand strategies for intercurrent events or the use of alternative analysis sets may be considered for supplementary analyses of study endpoints. For example, an imputation rule may be applied to compensate for missing data on the primary endpoint for exploratory purposes. [REDACTED]

This is an open-label study. Intermediate analysis on accumulating data (ie, disposition, baseline characteristics, description of primary and secondary endpoints, and safety data) may be conducted for publication purposes and periodic study monitoring.

Bar Index	Relative Length (approximate)
1	95
2	25
3	100
4	60
5	85
6	35
7	65
8	50
9	100
10	30
11	75
12	65
13	100

[illegible]

[illegible]

Endpoints based on validated clinician- and patient-reported assessments will be calculated according to instrument manuals. When defined in instrument manuals or published literature, achievement of the minimal clinically important difference or other clinically relevant change scores may be calculated and summarized.

Missing assessment results after premature study terminations, or for any other reasons (eg, lost to follow-up), will not be imputed for primary analysis.

Page 91

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and national regulatory authority (as applicable) before the study is initiated.
- Protocols and any amendments to the protocol will require IRB/IEC and national regulatory authority approval (as applicable) prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements (where applicable), Regulation (EU) 2016/679 General Data Protection Regulation (GDPR) requirements (where applicable), and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before any study activities were performed, unless otherwise allowed by protocol criteria, and must also include the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Appropriate steps will be taken to protect participants' personal data according to HIPAA, GDPR, and other local regulatory requirements, where applicable.
- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, and the ICF must describe how their personal data will be used.
- The participant must be informed that their medical records may be examined by clinical quality assurance auditors or other authorized personnel, or suppliers appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between the sponsor and study sites specifies the responsibilities of the parties' related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5. Committees Structure

A study-related steering committee (along with an associated charter) will be formed. This group will review and meet on an ad hoc basis to provide input on the protocol and significant study-related matters that arise and will assist with data interpretation at the conclusion of the study.

10.1.6. Dissemination of Clinical Study Data

As the sponsor of the study, Jazz Pharmaceuticals is solely responsible for disclosing results on ClinicalTrials.gov, EudraCT, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting requirements are solely the responsibility of the sponsor and agrees not to submit any information about the study or its results.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed CRF or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan or contracts.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or institution/site as applicable, for the period of time established in the clinical study agreement entered into by the investigators unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence regarding the identity of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. In addition, current medical records must be available.
- The definition of what constitutes source data can be found in the monitoring plan.
- The investigator must maintain accurate documentation (source data) supporting the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The first act of recruitment is the date that the first participant provides informed consent.

10.1.9.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

- Total number of participants enrolled

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor at least 30 days prior to submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 1. REFERENCES

American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-Third Edition (ICSD-3). Darien, IL: American Academy of Sleep Medicine; 2014. p. 53-62, 143-55.

Ahmed IM, Wu WP, Billiard M. Overview of Central Disorders of Hypersomnolence. Reference Module in Neuroscience and Biobehavioral Psychology. 2016.

Anderson KN, Pilsworth S, Sharples LD, et al. Idiopathic hypersomnia: a study of 77 cases. *Sleep*. 2007;30(10):1274-81.

Bassetti C, Aldrich MS. Idiopathic hypersomnia: a series of 42 patients. *Brain*. 1997;120(8):1423-35.

Bassetti CL, Adamantidis A, Burdakov D, et al. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Neurology*. 2019;15:519-39.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29(7):939-49.

Black J, Pardi D, Hornfeldt CS, et al. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. *Sleep Med*. 2009;10(8):829-35.

Black J, Pardi D, Hornfeldt CS, et al. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med*. 2010;6(6):596-602.

Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. *Sleep*. 2021;44(3):zsaa206.

Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. *Sleep*. 2009;32(7):915-9.

CMS.gov. CPAP For Obstructive Sleep Apnea. [cited 17 Oct 2023]. Available from: <https://www.cms.gov/medicare/coverage/evidence/cpap>.

Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, et al. Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. *Lancet Neurol*. 2022;21(1):53-65.

Dauvilliers Y, Roth T, Guinta D, et al. Effect of sodium oxybate, modafinil, and their combination on disrupted nighttime sleep in narcolepsy. *Sleep Med*. 2017;40:53-7.

Dauvilliers Y, Evangelista E, Barateau, et al. Measurement of symptoms in idiopathic hypersomnia. *Neurology*. 2019;92:e1754-62.

Dauvilliers Y, Barateau L, Lopez R, et al. Narcolepsy Severity Scale: a reliable tool assessing symptom severity and consequences. *Sleep*. 2020;20(20):1-11. doi:10.1093/sleep/zsaa009.

Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput*. 1985;17(6):652-5.

- Iverson GL, Lam RW. Rapid screening for perceived cognitive impairment in major depressive disorder. *Ann Clin Psychiatry*. 2013;25(2):135-40.
- Johns M. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540-5.
- Johns M. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*. 1992;15(4):376-81.
- Johns M. Sleepiness in different situations measured by the Epworth Sleepiness Scale. *Sleep*. 1994;17(8):703-10.
- Kaufmann H, Malamut R, Norcliffe-Kaufmann L, et al. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. *Clin Auton Res*. 2012;22:79–90.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606-13.
- Lavault S, Dauvilliers Y, Drouot X, et al. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. *Sleep Med*. 2011;12(6):550-6.
- Leu-Semenescu S, Quera-Salva MA, Dauvilliers Y. French consensus. Idiopathic hypersomnia: investigations and follow-up. *Rev Neurol (Paris)*. 2017;173:32-7.
- Maski KP, Colclasure A, Little E, et al. Stability of nocturnal wake and sleep stages defines central nervous system disorders of hypersomnolence. *Sleep*. 2021a;44(7):zsab021.
- Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2021b;17(9):1895-945.
- Maski K, Mignot E, Plazzi G, et al. Disrupted nighttime sleep and sleep instability in narcolepsy. *J Clin Sleep Med*. 2022;18(1):289-304.
- Morse AM, Chen A, Steininger TL, et al. Effects of lower-sodium oxybate on sleep time in a placebo-controlled, double-blind, randomised withdrawal study in adults with idiopathic hypersomnia. [abstract]. *Sleep Med*. 2022;100(1):S156.
- Mullington J, Broughton R. Daytime sleep inertia in narcolepsy-cataplexy. *Sleep*. 1994;17:69-76.
- Nittur N, Konofal E, Dauvilliers Y, et al. Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. *Sleep Med*. 2013;14(1):30-6.
- Ozaki A, Inoue Y, Hayashida K, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population. *Sleep Med*. 2012;13(2):200-6.
- Ozaki A, Inoue Y, Nakajima T, et al. Health-related quality of life among drug-naïve patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. *J Clin Sleep Med*. 2008;4(6):572-8.

- Pardi D, Black J. γ -Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs*. 2006;20(12):993-1018.
- Pizza F, Jaussent I, Lopez R, et al. Car crashes and central disorders of hypersomnolence: a French study. *PLoS One*. 2015a;10(6):e0129386.
- Pizza F, Ferri R, Poli F, et al. Polysomnographic study of nocturnal sleep in idiopathic hypersomnia without long sleep time. *J Sleep Res*. 2013;22:185-96.
- Plante DT. Nocturnal sleep architecture in idiopathic hypersomnia: a systematic review and meta-analysis. *Sleep Med*. 2018;45:17-24.
- Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-65.
- Roth T, Dauvilliers Y, Thorpy MJ, et al. Effect of FT218, a once-nightly sodium oxybate formulation, on disrupted nighttime sleep in patients with narcolepsy: results from the randomized phase III REST-ON trial. *CNS Drugs*. 2022;36(4):377-87.
- Roth T, Dauvilliers Y, Guinta D, et al. Effect of sodium oxybate on disrupted nighttime sleep in patients with narcolepsy. *J Sleep Res*. 2017;26(4):407-14.
- Roth T, Dauvilliers Y, Mignot E, et al. Disrupted nighttime sleep in narcolepsy. *J Clin Sleep Med*. 2013;9(9):955-65.
- Shahid A, Wilkinson K, Marcu S, et al. editors. STOP, THAT and one hundred other sleep scales. New York: Springer; 2012.
- Thorpy MJ, Arnulf I, Foldvary-Schaefer N, et al. Efficacy and safety of lower-sodium oxybate in an open-label titration period of a phase 3 clinical study in adults with idiopathic hypersomnia. *Nat Sci Sleep*. 2022;14:1901-17.
- Trotti LM. Waking up is the hardest thing I do all day: sleep inertia and sleep drunkenness. *Sleep Med Rev*. 2017;35:76-84.
- Trotti LM, Saini P, Bliwise DL, et al. Clarithromycin in γ -aminobutyric acid-related hypersomnolence: a randomized, crossover trial. *Ann Neurol*. 2015;78(3):454-65.
- Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. *Sleep*. 2009;32(6):753-9.
- Vernet C, Leu-Semenescue SM, Buzare MA, et al. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. *J Sleep Res*. 2010;19(4):525-34.
- Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835-43.
- XYREM International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med*. 2005;1(04):391-7
- XYREM (sodium oxybate) oral solution. US Prescribing Information. Jazz Pharmaceuticals, CA, USA. Apr 2023 (current at time of protocol development).

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution. US Prescribing Information. Jazz Pharmaceuticals, CA, USA. Apr 2023. (current at time of protocol development).

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution. PM. Jazz Pharmaceuticals, Dublin, Ireland. May 2023 (current at time of protocol amendment 3).

APPENDIX 2. CLINICAL LABORATORY TESTS

- The tests detailed in [Table 7](#) will be performed by the central laboratory.
- Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Table 7](#) of the protocol.
- Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table 7: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters		
Hematology	Complete blood count Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH Red cell distribution width % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry ^a	Albumin Alkaline phosphatase ^b ALT/SGPT AST/SGOT	Potassium Sodium Calcium Chloride Magnesium BUN Creatinine Gamma-glutamyl transferase	Total and direct bilirubin Total cholesterol Total protein Triglycerides Uric acid Thyroid stimulating hormone Glucose (nonfasting) Globulin
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)		
Pregnancy Testing	Highly sensitive serum pregnancy test (as needed for women of childbearing potential) at screening Urine pregnancy (dipstick) test (as needed for women of childbearing potential) at subsequent visits		

Laboratory Tests	Parameters
Other Screening Tests	Follicle-stimulating hormone and estradiol (as needed to confirm postmenopausal status) Breath alcohol test Urine drug screen

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

^a All events of ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (> 35% direct bilirubin) or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 (if INR measured) that may indicate severe liver injury (possible Hy's Law) must be reported to the sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

^b If alkaline phosphatase is elevated, consider fractionating.

NOTES: Investigators must document their review of each laboratory safety report.

APPENDIX 3. AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
<ul style="list-style-type: none"> • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Unsolicited and Solicited AE
<ul style="list-style-type: none"> • An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses that require hospitalization, an emergency room visit, or a visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
<ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition.

Events Meeting the AE Definition
<ul style="list-style-type: none"> • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> • Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
Results in death
<ul style="list-style-type: none"> • Is life-threatening • The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
<ul style="list-style-type: none"> • Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
<ul style="list-style-type: none"> Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
<ul style="list-style-type: none"> Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
<p>Other situations:</p> <p>Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.</p> <p>Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.</p>

Recording and Follow-up of AE and/or SAE

AE and SAE Recording
<ul style="list-style-type: none"> When an AE/SAE occurs, investigator is responsible for reviewing all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information. It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the required form. There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
<ul style="list-style-type: none"> The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

AE and SAE Recording

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
 - Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
 - Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
 - Life-threatening: life-threatening consequences; urgent intervention indicated.
 - Fatal: death related to AE
- These categories are based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 or higher.
 - When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts.
 - An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessments, the investigator will also consult the IB and/or product information, for marketed products
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

AE and SAE Recording
Follow-up of AEs and SAEs
<ul style="list-style-type: none"> • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor (or designee) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.
Reporting of SAE/ORE /Pregnancy Reports
Reporting to Sponsor or Designee through Electronic Data Collection Tool (via RSG)
<ul style="list-style-type: none"> • The primary mechanism for reporting an SAE/ORE/Pregnancy Report to sponsor or designee will be the electronic data collection tool (via RSG). • If the electronic data collection tool is unavailable, then the site will use the paper collection tool to report the event via email or fax within 24 hours to the sponsor or designee. • Initial notification via paper collection tool does not replace the need for the investigator to report an SAE/ORE/Pregnancy Report through the electronic data collection tool (via RSG). The site will enter the SAE/ORE/Pregnancy Report data into the electronic data collection tool as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/ORE/Pregnancy Report from a study participant or receives updated data on a previously reported SAE/ORE/Pregnancy after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE//ORE/Pregnancy form. • Contacts for SAE/ORE/Pregnancy reporting can be found in the site files.
Reporting to Sponsor or Designee via Paper Collection Tool When the Electronic Data Collection Tool (via RSG) is Not Utilized in the Study
<ul style="list-style-type: none"> • The primary mechanism for reporting an SAE/ORE/Pregnancy Report to sponsor or designee will be the paper collection tool (SAE/ORE/Pregnancy paper forms). • The site will complete the SAE/ORE/Pregnancy paper forms and report via email or fax within 24 hours to the sponsor or designee. • Email or fax is the preferred method of transmitting this information to the sponsor or designee.

- In rare circumstances and in the absence of email or fax, a copy of the SAE/ ORE/Pregnancy paper form may be sent by mail or courier service to the sponsor or designee.
- Contacts for SAE/ORE/Pregnancy reporting can be found in the site files.

APPENDIX 4. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

1. After menarche.
 2. From the time of menarche until becoming postmenopausal unless permanently sterile (defined as follows).
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
 - Females on HRT whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
 - Permanent sterilization methods (for the purpose of this study) include the following:
 - Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
 - For individuals with permanent infertility due to a medical cause other than those listed (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied when determining study entry.
- Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES ^a ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods ^b That Have Low User Dependency
<ul style="list-style-type: none">• Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c
<ul style="list-style-type: none">• Intrauterine device (IUD)

<ul style="list-style-type: none"> • Intrauterine hormone-releasing system (IUS)^c
<ul style="list-style-type: none"> • Bilateral tubal occlusion
<ul style="list-style-type: none"> • Azoospermic partner (vasectomized or due to a medical cause) • <i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i> Note: Documentation of azoospermia for a male participant can come from site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods^b That Are User Dependent
<ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation <ul style="list-style-type: none"> a. Oral b. Intravaginal c. Transdermal d. Injectable
<ul style="list-style-type: none"> • Progestogen-only hormone contraception associated with inhibition of ovulation^c <ul style="list-style-type: none"> ○ Oral ○ Injectable
<ul style="list-style-type: none"> • Sexual abstinence • <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i>

^a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

^b Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

^c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

APPENDIX 5. PROTOCOL AMENDMENT HISTORY

The protocol amendment summary of changes table for the current amendment is located directly before the TOC.

Amendment 02 (07 Nov 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and EU Regulation No 536/2014.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to update the analysis plan for the study, which now includes formal hypothesis testing. [REDACTED]

[REDACTED] The amendment also includes clarifications regarding weekly Titration Check-ins during the Flexible Titration Period for all participants.

These revisions, along with additional revisions for operational clarity and accuracy, are described in the table below. Minor editorial and formatting changes are not included.

Section # and Name	Description of Change	Brief Rationale
Title page	Added the EU Clinical Trial Number.	Update.
1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities 4.1. Overall Design 8.2.5. Clinician-Reported Dosing Form	Clarified that participants will require weekly Titration Check-ins during the Flexible Titration Period.	Clarification.
1.1. Synopsis 3. Objectives, Endpoints, and Estimands 9. Statistical Considerations	Added formal hypothesis testing for the narcolepsy and IH cohorts. Interim analysis text and subgroup analyses were also updated. Combined endpoints related to sleep stage shifts and separated endpoints related to nocturnal arousals and awakenings.	Statistical considerations and endpoints were updated to expand the analyses in the study.
1.1. Synopsis	Added “nighttime sleep architecture” to Synopsis study rationale.	Updated to align with new formal hypothesis testing.
1.1. Synopsis	[REDACTED] Removed any mention of PK assessments at select US study sites.	Correction/clarification. [REDACTED] [REDACTED] [REDACTED] [REDACTED] PK evaluations may be performed at any site with PK capabilities.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 1.2. Schema (Figure 1) 1.3. Schedule of Activities 4.1. Overall Design	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	Clarification.
[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]
1.1. Synopsis 1.3. Schedule of Activities [REDACTED] [REDACTED] 4.1. Overall Design 5. Study Population 8.5. Pharmacokinetics	Updated any language stating that PK evaluations are performed at sponsor-selected sites [REDACTED] [REDACTED].	Clarification; PK evaluations may be performed at any site with PK capabilities. Participants are not required to undergo PK evaluations in this study.
1.2. Schema	Added language to clarify the Flexible Titration Period.	Clarification.
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]
1.3. Schedule of Activities	Added 2 additional PK time points for participants who undergo PK evaluations.	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 4.1 Overall Design	Clarified that participants complete study activities at home during the SDP.	Clarification.
1.3. Schedule of Activities 8.2.1. Actigraphy	Added additional details about dispensing and collecting the actigraphy device.	Clarification.
1.3. Schedule of Activities	Tables were updated as follows: <ul style="list-style-type: none"> PVT text in notes was updated. PE and brief neurological assessments were separated into 2 separate rows. 	Clarifications.
1.3. Schedule of Activities 5.1. Inclusion Criteria	Text regarding the ESS was updated to clarify when the ESS is used to confirm eligibility.	Clarifications.
[REDACTED]	[REDACTED]	[REDACTED]
4.1. Overall Design 6.3. Assignment to Study Intervention 8. Study Assessments and Procedures 8.2.14. Polysomnography	Clarified that study staff should confirm participant eligibility during the Baseline Period before the participant may proceed to the Intervention Period.	Clarification.
4.1. Overall Design 8.2.14. Polysomnography 8.5. Pharmacokinetics	Added that the PK Visit is recommended to occur the night after the PSG Visit.	Recommendation (not a requirement).
5.2. Exclusion Criteria	Added an example of a significant medical condition that could impact sleep to exclusion criterion 8.	Clarification.
5.2. Exclusion Criteria 6.9. Concomitant Therapy	Updated exclusion criterion 10 (regarding exclusionary medications and substances) and added references to the list of prohibited medications in the Investigator Trial Site File.	Clarification.
5.2. Exclusion Criteria 8.3.3. Apnea/Hypopnea Index Appendix 1. References	Added a reference to the CMS.gov regarding the AHI.	Clarification.
5.3. Lifestyle Considerations 8.1.7. Participant/Site Check-in	Added/clarified guidance to sites regarding participant instructions.	Clarifications.

Section # and Name	Description of Change	Brief Rationale
5.4. Screen Failures	Added that rescreening may occur following a stable period (at least 1 month) after a change in medication and/or regimen.	Language was added to allow anyone who undergoes medication discontinuation or dose reduction for purposes of eligibility to rescreen.
6.9. Concomitant Therapy	Clarified that the use of concomitant alerting agents, and/or non-oxybate anticonvulsant medications is allowed at a stable dosage.	Clarification.
8.1.1. Informed Consent	Updated language to clarify that the investigator or qualified designee must obtain documented consent.	The qualified designee does not need a medical degree (if consistent with local regulations).
████████████████████ ██████	████████████████████ ████████████████████ ████████████████████ ████████████████████	██████████
8.2.2. Sleep Diary 8.2.4. Study Intervention Dosing Diary	Removed information regarding the collection of the last mealtime and caffeine use.	Correction; this information is collected in the Pre-PSG questionnaire.
████████████████████ ██████	████████████████████ ████████████████████ ██████████	██████████
8.3.2. Vital Signs	Clarified that HR measurements should also be recorded at intervals of 1 minute (similar to BP measurements). Redundant text was removed.	Clarification.
8.4.1. Time Period and Frequency for Collecting AE and SAE Information 8.4.3. Follow-up of AEs and SAEs	Clarified the investigator's obligation to follow up on the status of AEs and SAEs and update AE and SAE reports accordingly.	Clarification.
9.6. Sample Size Determination Appendix 1. References	Added a reference (Roth 2022) to support updated formal hypothesis testing.	Update to support expanded analyses in this study.
Appendix 1. References	Added reference for XYREM International Study Group 2005 study.	Correction; the reference was already cited in the document but was omitted from the reference list.
Appendix 3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.	Removed any mention of AEs of special interest and clarified Pregnancy Reports.	Clarification. Adverse events of special interest are not collected in this study.
Appendix 4. Contraceptive and Barrier Guidance	Updated the list of permitted contraceptive measures to include abstinence.	Abstinence is a permitted method of contraception if consistent with local regulations.

Amendment 01 (30 Jun 2023)

Overall Rationale for the Amendment:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Section # and Name	Description of Change	Brief Rationale
Title Page	[REDACTED]	[REDACTED]
1. STUDY SUMMARY	[REDACTED]	[REDACTED]
1.1. Synopsis	[REDACTED]	[REDACTED]
Table 1: Objectives, Endpoints, and Estimands	[REDACTED]	[REDACTED]
Table 2: Overall Study Design	[REDACTED]	[REDACTED]
1.2. Schema	<p>A time point (ie, 6 hours after first dose) was added to table of assessments for PK (now Table 5)</p> <p>Figure added (Figure 1): Study Entry Flow Diagram for Narcolepsy Cohorts</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>This time point was added to ensure at least 3 concentration-time points in the terminal phase are obtained.</p>
1.3. Schedules of Activities		
Table 3: Schedule of Assessments (Overall)		
Table 4: Schedule of Activities for Optional Overnight PK Visit (Twice Nightly Dosage/Narcolepsy Only)		
2. INTRODUCTION	[REDACTED]	
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS	[REDACTED]	
4. STUDY DESIGN		
5. STUDY POPULATION		
6. STUDY INTERVENTION(S) AND		

Section # and Name	Description of Change	Brief Rationale
CONCOMITANT THERAPY 8. STUDY ASSESSMENTS AND PROCEDURES Table 5: Study Treatment/Intervention 9. STATISTICAL CONSIDERATIONS		
1.3 Schedule of Activities	Explanation was added that the review of AEs, concomitant medications, and the Clinician-reported Dosing form includes weekly check-ins with the participant.	Clarification
4.2.1. Patient Input Into Design	Explanation was added that reporting of individual participant data will occur after the conclusion of the study.	Clarification
6.6. Dose Modifications	A statement was added that dose modifications will be recorded.	Clarification
8.3. Safety Assessments		
Physical Examinations	Height will be measured only at screening and at no other time.	Correction
Vital Signs	Participants do not have to be in a supine position when blood pressure is measured.	Correction
Pregnancy	Follow-up pregnancy testing will occur at a specific end-of-treatment time point.	Correction
APPENDIX 1: REFERENCES	The dates of the approved XYREM and XYWAV USPIs were updated.	USPIs were updated.
General	Terms were added to the List of Abbreviations.	Abbreviations were added and a term corrected.

Section # and Name	Description of Change	Brief Rationale
	In-text table numbers changed.	In-text tables were added.
	The correct name of the questionnaire is Patient Health Questionnaire-9, not Participant Health Questionnaire.	Correction
	Minor editorial changes were made as appropriate.	Clarity and consistency

INVESTIGATOR AGREEMENT

I have read the attached clinical protocol and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s), the United States FDA regulations relating to Good Clinical Practice and clinical trials, the EU Clinical Trials Directive (2001/20/EC), the EU GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation Tripartite Guidelines for GCP, where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the trial and for all trial-related medical decisions.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse or legal partner, or dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

Investigator Signatory:

Name:

Date

Title:

SPONSOR SIGNATORY

{Please see appended electronic signature page}

██████████ MD
Executive Director, Therapy Area Head, Neuroscience
Global Medical Affairs

Date

Medical monitor name and contact information can be found in the trial site binder (or equivalent).

Signature Page for JZP258-407-03 Protocol Amendment 3 Published
VV-CLIN-025158

Approval Task - Approval of Document Signing Verdict/Reason: I Approved This Document	<div></div> Medical Affairs 22-May-2024 00:30:58 GMT+0000
--	---

Signature Page for JZP258-407-03 Protocol Amendment 3 Published
VV-CLIN-025158