TITLE PAGE

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

Protocol Number: JZP258-406

Amendment Number: 04

Amendment Scope: Global

Compound: JZP258 (XYWAV)

Brief Title:

A Switch Study From High-Sodium Oxybate to XYWAV to Evaluate Changes in Blood Pressure in Participants With Narcolepsy

Study Phase: Phase 3/Phase 4

Sponsor Name: Jazz Pharmaceuticals, Inc.

Legal Registered Address: 3170 Porter Drive, Palo Alto, CA 94304

Regulatory Agency Identifier Number(s)

IND: [redacted]

EU Clinical Trial Number: 2023-504892-25-00

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 04	{Please see appended electronic signature page}
Amendment 03	14 Mar 2024
Amendment 02	06 Dec 2023
Amendment 01/EU 1	06 Nov 2023
Amendment 01	29 Mar 2023
Original Protocol	06 Feb 2023

Amendment 04 {Date: Please see appended electronic signature page}

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 Amendment 04 was to increase the upper limit of the screening SBP required for eligibility from 145 to 155 mm Hg. This updated criterion will expand the study population, which was originally defined by a narrow SBP range, to subserve clinical homogeneity in the sample. The narrow range for eligible SBP, coupled with the higher-than-anticipated screen failure rate, has been a potential barrier to enrollment and prompted this amendment. Increasing the upper SBP limit to 155 mm Hg is consistent with eligibility criteria used in other studies assessing the impact of dietary sodium reduction on BP (eg, 159, 160 mm Hg; Sacks, 2001; Juraschek, 2017; Gupta, 2023). In addition, results of this study with an expanded SBP range are more likely to be representative of study populations that demonstrated an increased prevalence of hypertension in narcolepsy (Ohayon, 2013; Tessier-Sherman, 2013; Black 2017; Ben-Joseph, 2023).

The eligibility criteria were also updated to clarify that participants must be taking high-sodium oxybate with twice-nightly dosing at study entry and exclude participants with resistant hypertension. In addition, the amendment includes 2 new laboratory tests (urine potassium and microalbumin) to supplement the interpretation of core data. Finally, the number of participants expected to enroll (ie, sign the ICF) was increased to align with the high observed screen failure rate. Additional changes were made throughout the protocol for operational clarity. A description of changes is provided below. Minor editorial changes have not been summarized in the table.

Section # and Name	Description of Change	Brief Rationale
• 1.1 Synopsis • 3 Objectives, Endpoints, and Estimands • 4.1 Overall Design • 4.2 Scientific Rationale for Study Design • 5.1 Inclusion Criteria	The upper limit of the average screening SBP required for eligibility was increased from 145 to 155 mm Hg.	This change was made to support study recruitment. This update will expand the participant population for whom a switch from twice-nightly high-sodium oxybate to XYWAV may be relevant, as it includes a broader range of hypertension (ie, a screening SBP between 130 and 155 mm Hg [inclusive]).
• 1.2 Schema • 1.3 Schedule of Activities • 4.1 Overall Design • 8.2.1 24-Hour Blood Pressure Monitoring	Updated the definition for 24-hour BP recording minimum data quality standards.	Update.
• 1.3 Schedule of Activities • 5.1 Inclusion Criteria • 8.3.2.1 Blood Pressure and Other Vitals	Clarified that OBPM may be repeated up to 2 additional times during the screening visit using the sponsor-provided device (which automatically records in triplicate). Thus, up to 3 triplicate BP recordings may be collected at the Screening Visit.	The OBPM may be repeated up to 2 additional times at the Screening Visit to account for temporary fluctuations in BP.
• 1.1 Synopsis • 9.5 Sample Size Determination	Updated the number of participants expected to enroll (ie, sign the ICF) in this study.	Enrollment numbers were updated to account for the observed screen failure rate.
• 1.3 Schedule of Activities • 8.2.3 Sleep and Study Intervention Dosing Diaries	Clarified that site personnel must initialize diaries and specified visits and review diary data entries.	Clarification.
• 4.1 Overall Design • 8.2.1 24-Hour Blood Pressure Monitoring	Clarified that participants will wear the ambulatory BP device for approximately 25 hours to ensure that 24 hours of data are captured.	Clarification.
• 5.2 Exclusion Criteria • 8.3.3 Electrocardiograms	Clarified that investigators must review ECG results.	Clarification.
• 9.1 Statistical Hypotheses • 9.3.2 Primary Endpoint	Harmonized symbols representing the difference in the 24-hour SBP from baseline to EOT.	Correction.

Section # and Name	Description of Change	Brief Rationale
• 5.1 Inclusion Criteria • 5.2 Exclusion Criteria	Added an exclusion criterion for participants with resistant hypertension. References to the new exclusion criterion were added to relevant inclusion criteria.	Resistant hypertension represents a distinct subgroup of hypertension that may not be representative of the intended study population.
• 1.1 Synopsis	Updated the anticipated number of study sites.	Update.
• 1.3 Schedule of Activities	Clarified that post-study-intervention treatment information will only be collected for participants in the US. Rearranged and/or combined rows in the SoA for clarity.	Clarifications.
• 3 Objectives, Endpoints, and Estimands	Corrected text for the following endpoint: change from baseline to EOT Visit on the seated resting average SBP (mm Hg).	Correction; text previously referred to an End of Intervention Visit.
• 5.1 Inclusion Criteria	Clarified that participants in this study must be taking a high-sodium oxybate with twice-nightly dosing at study entry.	Clarification; the study includes a 1-day switch from high-sodium oxybate with twice-nightly dosing to XYWAV with twice-nightly dosing, which is consistent with recommendations in the XYWAV USPI.
• 5.2 Exclusion Criteria	Clarified and refined exclusion criteria language regarding cardiovascular disease.	Language was updated to clarify that participants with chronic/persistent atrial fibrillation are not eligible for the study.
• 6.6 Dose Modification	Clarified that a participant's total nightly dose should be 6 to 9 g/night (inclusive).	Clarification.
• 6.9 Concomitant Therapy	Corrected cross-references to inclusion criteria 4 and 5.	Correction.
• 8.1.4 Medication Review (Prior and Concomitant Medications)	Clarified instructions regarding the medication review and removed statement regarding medication washout.	Clarification. Medication washout is not required in this study.

Section # and Name	Description of Change	Brief Rationale
• 8.2.1 24-Hour Blood Pressure Monitoring	Updated language to state that the same device *should* be used to collect each 24-hour BP recording.	Every effort should be made to use the same device for each 24-hour BP recording, although this may not always be possible (eg, in cases of device failure).
• 8.3.2.1 Blood Pressure and Other Vitals	Clarified that BP and pulse measurements should be preceded by at least 5 minutes of quiet rest, with no talking. Added language to describe the sponsor-provided OBPM device.	Clarifications.
• 8.4.5 Pregnancy	Added that in the event of a pregnancy, neonates will be followed until 6 months after birth.	Text was added to align with the sponsor's procedures.
• 9.2 Analysis Sets	Renamed "Modified Intent-to-Treat (Completer Set)" as "Completer Set" and added the Effectiveness Set	Alignment with SAP.
• Appendix 1 References	Added new literature references.	New references were added to support the amendment rationale.
• Appendix 2 Clinical Laboratory Tests	Removed text indicating that tests detailed in Table 7 are for screening purposes only. Updated Table 7 to include laboratory parameters for 24-hour urine (urine sodium and urine creatine) and eGFR. Clarified in Table 7 that the urine pregnancy test would be performed via an *office- or home-based* dipstick. Added laboratory tests for urine potassium and microalbumin.	Corrections; laboratory tests collected at time points specified in the SoA. The table previously omitted laboratory tests for eGFR, urine sodium, and urine creatinine. Clarification; decentralized participants may take urine pregnancy tests at home. Urine potassium and microalbumin laboratory tests were added to supplement the interpretation of core data.
• Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removed any mention of AEs of special interest.	This study does not specify AEs of special interest; thus, reports for AEs of special interest are not needed.

Section # and Name	Description of Change	Brief Rationale
• Throughout	Clarified that "high-sodium oxybate" in this protocol refers to high-sodium oxybate with twice-nightly dosing.	Clarification.

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LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ACC	American College of Cardiology
ADL	Activities of daily living
AE	Adverse event
AHA	American Heart Association
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
C-SSRS	Columbia – Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early discontinuation
EDS	Excessive daytime sleepiness
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GHB	Gamma hydroxybutyrate
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's brochure
ICF	Informed consent form

Abbreviation or Term	Definition/Explanation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders – Third Edition
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NASEM	National Academies of Sciences, Engineering, and Medicine
NT1	Type 1 narcolepsy
NT2	Type 2 narcolepsy
OBPM	Office blood pressure measurement
OR	Odds ratio
ORE	Other reportable experience
PGIc	Patient Global Impression of Change
PGIs	Patient Global Impression of Severity
REM	Rapid eye movement
RSG	RAVE Safety Gateway
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SFU	Safety follow-up
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SOC	System Organ Class
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
V	Visit
WOCBP	Woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Brief Title:

A Switch Study From High-Sodium Oxybate to XYWAV to Evaluate Changes in Blood Pressure in Participants With Narcolepsy

Regulatory Agency Identifier Number(s):

IND: [redacted]
EU Clinical Trial Number: 2023-504892-25-00

Rationale:

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution was developed as an alternative low-sodium formulation for XYREM (sodium oxybate) and 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 dose range of 6 to 9 g nightly. The lower sodium content in XYWAV compared to twice-nightly high-sodium oxybate (eg, XYREM) may result in a reduction in blood pressure, which may lead to a lower risk of hypertension and other related cardiovascular diseases.

Objectives and Endpoints and Estimands:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on 24-hour ambulatory SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the 24-hour average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the 24-hour average SBP (mm Hg)

Objectives	Endpoints
Secondary Efficacy	
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on daytime ambulatory SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the daytime average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the daytime average SBP (mm Hg)
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on seated resting SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the seated resting average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the seated resting average SBP (mm Hg)
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on nighttime SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the nighttime average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the nighttime average SBP (mm Hg)

Objectives	Endpoints
Exploratory Efficacy	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Safety	
To evaluate safety in participants switching from twice-nightly high-sodium oxybate to XYWAV	• Overall TEAEs • TEAEs by maximum severity • TEAEs related to study intervention • Serious TEAEs • TEAEs leading to discontinuation • Fatal TEAEs

Abbreviations: AE = adverse event; BP = blood pressure; DBP = diastolic blood pressure; EOT = end of treatment; PGIc = Patient Global Impression of Change; PGIs = Patient Global Impression of Severity; SBP = systolic blood pressure; TEAE = treatment-emergent adverse event.

Brief Summary:

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

Overall Design:

Study JZP258-406 is a multicenter, single-arm, open-label switch study. The study will enroll individuals diagnosed with Type 1 or Type 2 narcolepsy [redacted]. In regions where XYWAV follows approved label, the protocol is a Phase 4 interventional study, and in regions where XYWAV does not follow approved label, the protocol is a Phase 3 study.

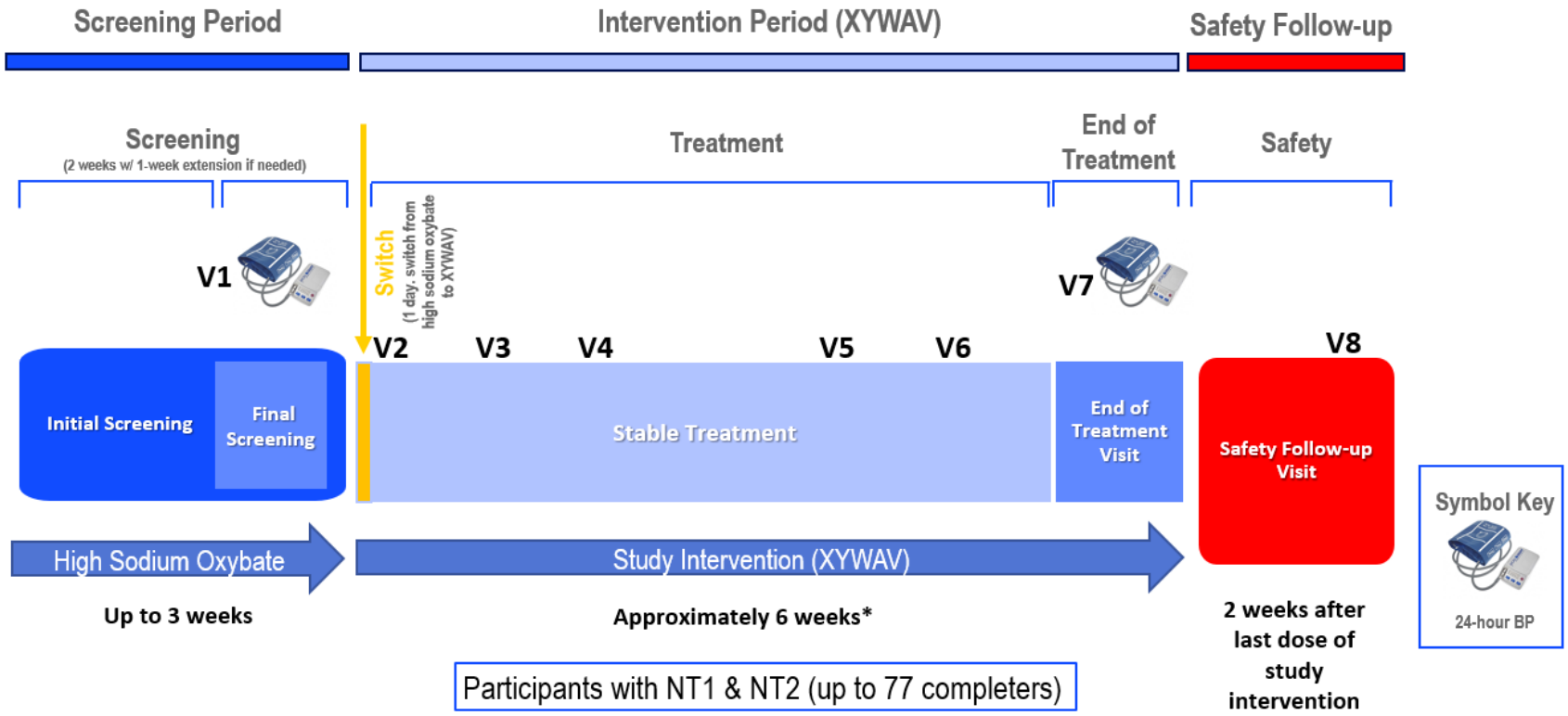
Table 2: Overall Study Design

Study Phase	Phase 3/Phase 4
Clinical Indication	Narcolepsy
Study Type	Interventional
Type of Design	Open-label, single-arm switch study
Type of Control	None
Study Blinding	N/A, open-label
Population	The study will include participants 18 to 70 years of age with a diagnosis of Type 1 or Type 2 narcolepsy that meets ICSD-3 criteria or DSM-5 criteria, who have been receiving 6 to 9 g/night (inclusive) of twice-nightly high-sodium oxybate for ≥ 6 consecutive weeks [redacted].
Number of Study Sites	Up to approximately 60 study sites worldwide are anticipated to enroll participants in this study.
Number of Participants	This study will use a sequential design in which the sample size is not fixed, and data will be evaluated during a planned interim analysis to determine the final study sample size. Thus, the sample size is presented as a range that depends on the results of the interim analysis. The sample size also accounts for a 60% screen failure rate after enrollment (ie, signing the ICF) during the Screening Period and assumes a 15% discontinuation/withdrawal rate during the Intervention Period.

	Based on these assumptions, approximately 170 (up to approximately 230) study participants will enroll to enable a minimum of 67 (up to approximately 91) to initiate treatment with the study intervention (ie, switch to XYWAV) and to capture complete data (both during the Screening Period and at the EOT Visit) for a minimum of 57 participants (up to approximately 77).
Duration of Participation	The study includes the following study periods: a Screening Period (up to 3 weeks), an Intervention Period (approximately 6 weeks, initiated by the switch from twice-nightly high-sodium oxybate to XYWAV) that includes approximately 6 weeks of treatment, an EOT Visit, and a Safety Follow-up Visit (at least 2 weeks after the last dose of study intervention). The study duration for each participant will be up to approximately 11 weeks. From the start of the Intervention Period through the Safety Follow-Up Visit, each participant will take approximately 8 weeks to complete their study participation.
Treatment Duration	Approximately 6 weeks
Visit Frequency	Participants will attend up to 8 scheduled visits during this study (visit schedules are specified in the SoA [Section 1.3]). This will be a hybrid study to allow participants to enroll either virtually (decentralized participants) or at an investigational site (site-based participants). Decentralized participants are participants who are enrolled virtually and who will not have any assessments performed physically at an investigational site. Site-based participants are participants who are enrolled at an investigational site and will have some assessments performed at that site. For all participants (both decentralized and site-based), some visits will be conducted entirely by telemedicine. For decentralized participants, some assessments will require in-person presence of study personnel at the participant's location. Details are provided in the SoA (Section 1.3).
Number of Treatment Arms	1
Treatment Groups	XYWAV (6 to 9 g/night)
Data Monitoring Committee	A data monitoring committee is not planned for this study. A steering committee will be assembled for this study.

Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EOT = End of Treatment; ICF = Informed consent form; ICSD-3 = International Classification of Sleep Disorders - Third Edition; SBP = Systolic blood pressure; SoA = Schedule of Activities.

1.2. Schema



Abbreviations: BP = blood pressure; EOT = end of treatment; NT1 = Type 1 narcolepsy; NT2 = Type 2 narcolepsy.
*Participants will continue taking study intervention until the EOT 24-hour BP recording meets minimum data quality standards (defined in Section 8.2.1). If needed, participants may repeat the EOT 24-hour BP recording up to 2 additional times, which would increase the overall duration of the Intervention Period.

1.3. Schedule of Activities

Table 3: Schedule of Assessments – Site-Based Participants

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
		Switch to XYWAV					End of Treatment Visit			• Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders) • The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit.
Study Visits	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7[a]**		**V8**	Additional unscheduled visits will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after the last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, Day –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Informed consent	X									
Inclusion/exclusion criteria	X	X								Confirm that participant continues to meet eligibility criteria and that screening 24-hour BP measurement meets quality control criteria before switching to XYWAV.
Demographics	X									
Medical history	X									
Physical examination	X									Refer to Section 8.3.1.
Vital signs (OBPM, pulse, height, weight)	X*			X	X		X	X		Triplicate OBPM and pulse rate recordings are collected and averaged automatically using the sponsor-provided device. *At the Screening Visit, triplicate OBPM and pulse rate recordings may be repeated up to 2 additional times (Refer to Section 8.3.2). *Height only required at screening.
Electrocardiogram	X						X	X		
Clinical labs	X									
Serum pregnancy test (WOCBP only)	X									Serum test at screening as assessed by a central laboratory.
Urine pregnancy test (WOCBP only)		X					X	X		Urine tests (dipstick) may be performed at additional study visits, if needed.

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
		Switch to XYWAV					End of Treatment Visit			• Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders) • The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit.
Study Visits	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7[a]**		**V8**	Additional unscheduled visits will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after the last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, Day –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
24-Hour urine collection	X						X	X		Should occur within 72 hours of the 24-hour BP recording (can be extended to 1 week if necessary). Must occur (but results do not need to be available) before the switch to XYWAV.
24-Hour BP monitoring[a]	X						X	X		• Screening recording should occur after all eligibility criteria are met (but laboratory results do not need to be available) and ≤ 2 weeks prior to the switch to XYWAV. • Participants must return device within 3 days after the conclusion of the recording (which will require an additional site visit). • Refer to Section 8.2.1.
Participant instructions	X	X	X	X	X	X	X	X	X	
Sleep diary	X					X	X	X		• To be completed daily for approx 7 days around the time of (and including) each 24-hour BP recording. • To be completed concurrently with the study intervention dosing diary. • Site personnel should initialize diary at each specified visit and review diary data entries during each approx 7-day period. • Refer to Section 8.2.3.

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
		Switch to XYWAV					End of Treatment Visit			• Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders) • The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit.
Study Visits	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7[a]**		**V8**	Additional unscheduled visits will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after the last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, Day –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Study intervention dosing diary	X					X	X	X		• Before the switch to XYWAV (ie, at screening), diary will capture the use of twice-nightly high-sodium oxybate. • To be completed daily for approx 7 days around the time of (and including) each 24-hour BP recording. • To be completed concurrently with the sleep diary. • Site personnel should initialize diary at each specified visit and review diary data entries during each approx 7-day period. • Refer to Section 6.5 and Section 8.2.3.
C-SSRS	X									Administered by qualified site rater.
PGIs	X						X	X		
PGIc							X	X		
AE/SAE reporting		X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Dispense study intervention (XYWAV)		X		X	X		X			
Start XYWAV dosing		X								
Study intervention compliance review				X	X		X	X		Refer to Section 6.5.
Collect post–study intervention narcolepsy treatment information									X	This information will only be collected for participants in the US.

Abbreviations: AE = adverse event; approx = approximately; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; E/D = early discontinuation; EOT = end of treatment; OBPM = office blood pressure measurement; PGIc = Patient Global Impression of Change; PGIs = Patient Global Impression of Severity; SAE = serious adverse event; SFU = safety follow-up; V = visit; WOCBP = woman of childbearing potential.

[a] Unscheduled visits will be needed (eg, for repeating the 24-hour BP assessment [if needed; up to 2 additional times], returning the BP recording device, or another reason per the investigator's discretion). Quality control criteria for 24-hour BP recordings are defined in Section 8.2.1.

Table 4: Schedule of Assessments – Decentralized Participants

Procedure	**Screening Period (twice-nightly high-sodium oxybate)**	**Intervention Period (XYWAV) Telemedicine Visits shaded in gray**						**E/D**	**Safety Follow-up Visit**	**Notes** • The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit. • Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders).
NOTE: X = assessments that can occur via telemedicine. O = assessments that must occur face-to-face (with study personnel at the participant's location).		**Switch to XYWAV**					**End of Treatment Visit**			
Study Visits	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7[a]**		**V8**	Additional unscheduled visits at the participant's home location will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Informed consent	X									
Inclusion/exclusion criteria	X	X								Confirm that participant continues to meet eligibility criteria and that screening 24-hour BP measurement meets quality control criteria before switching to XYWAV.
Demographics	X									
Medical history	X									
Physical examination	O									Refer to Section 8.3.1.
Vital signs (OBPM, pulse, height, weight)	O*						O	O		Triplicate OBPM and pulse rate recordings are collected and averaged automatically using the sponsor-provided device. *At the Screening Visit, triplicate OBPM and pulse rate recordings may be repeated up to 2 additional times (Refer to Section 8.3.2). *Height only required at screening. Study personnel will provide an electronic scale for use at the participant's location.

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
NOTE: X = assessments that can occur via telemedicine. O = assessments that must occur face-to-face (with study personnel at the participant's location).		Switch to XYWAV					End of Treatment Visit			• The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit. • Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders).
Study Visits	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**[a]		**V8**	Additional unscheduled visits at the participant's home location will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Electrocardiogram	O						O	O		
Clinical labs	O									
Serum pregnancy test (WOCBP only)	O									Serum test at screening as assessed by a central laboratory.
Urine pregnancy test (WOCBP only)		X					X	X		Urine tests (dipstick) may be performed at additional study visits, if needed; can be performed at the participant's location with results confirmed by study personnel.
24-Hour urine collection	X						X	X		Should occur within 72 hours of the 24-hour BP recording (can be extended to 1 week if necessary). Must occur (but results do not need to be available) before the switch from twice-nightly high-sodium oxybate to XYWAV.
24-Hour BP monitoring[a]	O						O	O		• Screening recording should occur after all eligibility criteria are met (but laboratory results do not need to be available) and ≤ 2 weeks prior to the switch to XYWAV. • Study staff will return within 3 days after the conclusion of the recording (which would require an additional visit). • Refer to Section 8.2.1.
Participant instructions	X	X	X	X	X	X	X	X	X	

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
NOTE: X = assessments that can occur via telemedicine. O = assessments that must occur face-to-face (with study personnel at the participant's location).		**Switch to XYWAV**					**End of Treatment Visit**			• The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit. • Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders).
Study Visits	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**[a]		**V8**	Additional unscheduled visits at the participant's home location will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Sleep diary	X					X	X	X		• To be completed daily for approx 7 days around the time of (and including) each 24-hour BP recording. • To be completed concurrently with the study intervention dosing diary. • Site personnel should initialize diary at each specified visit and review diary entries during each approx 7-day period. • Refer to Section 8.2.3.
Study intervention dosing diary	X					X	X	X		• Before the switch to XYWAV (ie, at screening), diary will capture the use of twice-nightly high-sodium oxybate. • To be completed daily for approx 7 days around the time of (and including) each 24-hour BP recording. • To be completed concurrently with the sleep diary. • Site personnel should initialize diary at each specified visit and review diary entries during each approx 7-day period. • Refer to Section 6.5 and Section 8.2.3.
C-SSRS	X									Administered by qualified site rater.
PGIs	X						X	X		
PGIc							X	X		
AE/SAE reporting	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	

Procedure	Screening Period (twice-nightly high-sodium oxybate)	Intervention Period (XYWAV) Telemedicine Visits shaded in gray						E/D	Safety Follow-up Visit	Notes
NOTE: X = assessments that can occur via telemedicine. O = assessments that must occur face-to-face (with study personnel at the participant's location).		Switch to XYWAV					End of Treatment Visit			• The E/D Visit should be scheduled as soon as possible after a participant discontinues study intervention and/or study. Participants should be asked to complete as many assessments as possible during this visit. • Telemedicine visits: All remote visits using various media (eg, telephone, video calls, and email reminders).
Study Visits	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**[a]		**V8**	Additional unscheduled visits at the participant's home location will be needed[a].
Scheduled Day(s)	**-14**	**1**	**7**	**14**	**28**	**35**	**42***		**56****	*Study intervention to be taken each night until the EOT 24-hour BP assessment has met minimum data quality standards[a]. **SFU Visit should occur 14 days (+ 3 days) after last dose of study intervention or E/D Visit (as applicable).
Study Visit Window (days)	**–7 (ie, –21)**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**+ 3**	
Dispense study intervention (XYWAV)	X			X	X		X			Study intervention will be shipped to participants who have met all eligibility criteria, with the first shipment prior to Visit 2. Participants should acknowledge receipt before initiating the switch to XYWAV.
Start XYWAV dosing		X								
Study intervention compliance review				X	X		X	X		Refer to Section 6.5.
Post–study intervention narcolepsy treatment information.									X	This information will only be collected for participants in the US.

Abbreviations: AE = adverse event; approx = approximately; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; E/D = early discontinuation; EOT = end of treatment; OBPM = office blood pressure measurement; PGIc = Patient Global Impression of Change; PGIs = Patient Global Impression of Severity; SAE = serious adverse event; SFU = safety follow-up; US = United States; V = visit; WOCBP = woman of childbearing potential.

[a] Unscheduled visits will be needed that require in-person presence of study personnel at the participant's home location (eg, for reviewing the BP recording, repeating the 24-hour BP assessment [if needed; up to 2 additional times], collecting the BP recording device, or another reason per the investigator's discretion). Quality control criteria for 24-hour BP recordings are defined in Section 8.2.1.

2. INTRODUCTION

XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution (also referred to as JZP258) was developed as an alternative low-sodium formulation for XYREM (sodium oxybate) and 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 dose range of 6 to 9 g nightly.

2.1. Study Rationale

The aim of this study is to quantify the change in 24-hour average SBP when participants with narcolepsy treated with twice-nightly high-sodium oxybate are transitioned to XYWAV. Assessments, including ambulatory SBP and DBP, will be obtained during the Screening Period and again during the EOT Visit. It is hypothesized that there will be a clinically relevant reduction of SBP after switching from twice-nightly high-sodium oxybate to XYWAV. The results of this study are anticipated to provide HCPs, patients, and payers with important new information regarding BP changes related to differences in sodium content between available oxybates for the treatment of narcolepsy.

2.2. Background

Narcolepsy is a life-long neurologic disease for which no cure has been identified. The worldwide prevalence of narcolepsy is estimated to be 0.02% to 0.067% (Ohayon, 2007), and in the US, the disease afflicts approximately 1 in 2000 individuals (Majid, 2010). Narcolepsy has been defined as a REM sleep disorder resulting from dysregulation of the sleep-wake cycle (Nishino, 2007). It is characterized by pathological sleepiness, commonly termed excessive daytime sleepiness or EDS, and includes disrupted nighttime sleep and abnormal REM sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations (Boscolo-Berto, 2012; Dauvilliers, 2012).

XYREM (sodium oxybate) has been available in the US since 2002 and is indicated in the US for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy (XYREM USPI). XYREM is also approved in Canada for the treatment of cataplexy in patients with narcolepsy (XYREM Canadian Product Monograph) and in the EU (XYREM EU SmPC) for the treatment of narcolepsy with cataplexy in adult patients, adolescents, and children from the age of 7 years.

While XYREM has been shown to have a positive risk-benefit profile when prescribed per recommended label and has been designated as standard of care for the treatment of cataplexy and EDS by the American Academy of Sleep Medicine (Morgenthaler, 2007), the current formulation of XYREM imparts a significant amount of additional sodium to an individual's daily dietary salt intake. The AHA and FDA have recommended an intake of no more than 2300 mg of sodium per day, with an ideal limit of no more than 1500 mg per day for most adults (FDA, 2016; AHA, 2018).

An increased risk of cardiovascular disease has been causally associated with high sodium intake (Whelton, 2012; FDA, 2016; NASEM, 2019a; Zeng, 2022). Administration of the maximum

recommended daily dose of XYREM (9 g/day) results in an intake of 1640 mg sodium/day, akin to 109% of the ideal recommended dietary allowance of sodium per day (CDC, 2010). XYREM product labeling includes warnings and precautions regarding this high sodium content, advising monitoring of patients with heart failure, hypertension, or impaired renal function (XYREM USPI). This may limit certain patients with these existing conditions from receiving oxybate therapy, as an increase in sodium intake enhances risk for cardiovascular morbidity and mortality, particularly in these at-risk individuals (Cook, 2007).

Many patients with narcolepsy have associated cardiovascular risk factors and comorbidities (Ohayon, 2014; Jennum, 2021), and an analysis of US claims data revealed that multiple conditions were more common in patients with narcolepsy, including acute myocardial infarction (OR 1.6), coronary atherosclerosis (OR 2.2), and congestive heart failure (OR 2.6) (Black, 2017). Narcolepsy is also associated with a blunted nocturnal sleep-related decrease in BP (nondipping phenomenon) (Dauvilliers, 2012). In the general population, this has been shown to confer increased cardiovascular risk independent of a diagnosis of hypertension (Ohkubo, 2002).

Existing evidence suggests that reducing daily sodium intake by 1000 to 1500 mg/day can substantially reduce cardiovascular risk (Bibbins-Domingo, 2010; Coxson, 2013; NASEM, 2019b). In addition, chronic use of medications with relatively high sodium content has been shown to significantly impact overall cardiovascular health. For instance, studies of participants who regularly use sodium-containing paracetamol formulations have demonstrated that switching to sodium-free paracetamol formulations (thus reducing daily sodium intake by approximately 1500 to 1600 mg/day) was associated with significant reductions in SBP and DBP (Ubeda, 2009; Benitez-Camps, 2018). Therefore, reducing daily sodium intake by approximately 1000 to 1500 mg/day, either through changes in diet or changes in medications, has been shown to result in clinically meaningful improvements in cardiovascular health.

XYWAV, an alternative low-sodium formulation for XYREM, has been approved in the US for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy and is also approved for the treatment of idiopathic hypersomnia in adults in the US (XYWAV USPI). At the recommended dose range of 6 to 9 g/night, XYREM contains 1100 to 1638 mg sodium, compared with 87 to 131 mg in XYWAV at the same dose range. The reduction in daily sodium associated with a switch from twice-nightly high-sodium oxybate (such as XYREM) to XYWAV (ie, by 1013 to 1507 mg/day) is hypothesized to result in a reduction in BP, which may lead to a lower risk of hypertension and other related cardiovascular diseases.

2.3. Benefit/Risk Assessment

A summary of the benefit-risk assessment for conducting Study JZP258-406 is provided in the subsections that follow.

2.3.1. Risk Assessment

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

- Participants may experience reduced tolerability for XYWAV compared with twice-nightly high-sodium oxybate.
- Participants may experience study procedure–related risks and/or discomfort, including risks and/or discomfort associated with clinical laboratory assessments or the ECG (eg, due to ECG leads).
- Participants may experience discomfort from wearing the ambulatory BP device during each 24-hour recording.

2.3.2. Benefit Assessment

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

- Participants may experience improved tolerability with XYWAV relative to twice-nightly high-sodium oxybate.
- Participants switching from twice-nightly high-sodium oxybate to XYWAV may experience reduced BP and a reduction in the cardiovascular risks associated with higher levels of sodium consumption.

2.3.3. Overall Benefit/Risk Summary

Benefits to participants include receiving a lower sodium alternative to their current therapy that may lower BP while continuing to alleviate symptoms of narcolepsy. Risks include those associated with study procedures, as well as those associated with the administration of XYWAV (which are expected to be similar to those seen in prior clinical studies and in the postmarketing setting). More detailed information about the known and expected benefits and risks and reasonably anticipated TEAEs of XYWAV is provided in the USPI (XYWAV USPI).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary Efficacy	
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on 24-hour ambulatory SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the 24-hour average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the 24-hour average SBP (mm Hg)
Secondary Efficacy	
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on daytime ambulatory SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the daytime average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the daytime average SBP (mm Hg)
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on seated resting SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted]

Objectives	Endpoints
	Endpoint: Change from baseline to EOT Visit on the seated resting average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the seated resting average SBP (mm Hg)
To evaluate the impact of switching from twice-nightly high-sodium oxybate to XYWAV on nighttime SBP for participants with narcolepsy	The **estimand** is defined as follows: **Treatments:** XYWAV **Population:** Participants with Type 1 or Type 2 narcolepsy, treated with 6 to 9 g (inclusive) of twice-nightly high-sodium oxybate per evening, [redacted] **Endpoint:** Change from baseline to EOT Visit on the nighttime average SBP (mm Hg) **Intercurrent events:** Alternative/additional or changes in therapy related to BP as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events will be provided. Participants who experience any intercurrent event will be included in the analysis. **Summary:** Change from baseline to EOT Visit on the nighttime average SBP (mm Hg)
Exploratory Efficacy	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Safety	
To evaluate safety in participants switching from twice-nightly high-sodium oxybate to XYWAV.	• Overall TEAEs • TEAEs by maximum severity • TEAEs related to study intervention • Serious TEAEs • TEAEs leading to discontinuation • Fatal TEAEs

Abbreviations: AE = adverse event; BP = blood pressure; DBP = diastolic blood pressure; EOT = end of treatment; PGIc = Patient Global Impression of Change; PGIs = Patient Global Impression of Severity; SBP = systolic blood pressure; TEAE = treatment-emergent adverse event.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, single-arm, open-label switch study**.** The study will enroll individuals diagnosed with Type 1 or Type 2 narcolepsy [redacted]. In regions where XYWAV follows the approved label, the protocol is a Phase 4 interventional study, and in regions where XYWAV does not follow the approved label, the protocol is a Phase 3 study. Upon signing the ICF, participants will be considered enrolled. Participants who consent to participate in the study will be screened based on the inclusion and exclusion criteria.

Participants will be asked to be on 6 to 9 g/night of high-sodium oxybate with twice-nightly dosing for ≥ 6 consecutive weeks prior to screening. After all other eligibility criteria have been assessed (with the exception of clinical laboratory results obtained at screening), the 24-hour BP recording can be initiated and the 24-hour urine collection obtained. After all screening assessments have been completed, eligible participants will switch, on a gram-for-gram basis, from twice-nightly high-sodium oxybate (eg, XYREM) to XYWAV. This switch must occur no more than 2 weeks after the 24-hour ambulatory BP recording. After approximately 6 weeks of treatment with XYWAV, the 24-hour BP recording and 24-hour urine collection, along with other measurements noted in the SoA (Section 1.3), will be repeated during the EOT Visit. Study participation will end following a Safety Follow-Up Visit.

Participants taking stimulants and/or alerting agents or other medications known to affect BP may do so for the duration of the study if doses were unchanged for at least 2 months prior to study entry and remain unchanged throughout the study period. Participants taking antihypertensives at study entry must agree to maintain their treatment at the same dose throughout the study unless otherwise advised by their medical care provider. Any changes to these therapies during the course of the study will be reported (refer to Section 6.9).

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

- A Screening Period (up to 3 weeks).
- An Intervention Period (approximately 6 weeks): this period is initiated by the switch from twice-nightly high-sodium oxybate to XYWAV and includes approximately 6 weeks of treatment with the study intervention (XYWAV) and an EOT Visit.
  - Participants will continue taking study intervention until the EOT 24-hour BP recording meets minimum data quality standards (quality control criteria are defined in Section 8.2.1). If needed, participants may repeat the EOT 24-hour BP recording up to 2 additional times, which would increase the duration of the Intervention Period and, consequently, the overall duration of study participation.
  - After completing an EOT 24-hour BP recording that meets minimum data quality standards, participants may transition to commercial XYWAV (as permitted by local health authorities) or other standard of care per physician discretion.

- A Safety Follow-up Visit (to be scheduled at least 14 days after the last dose of study intervention).

This will be a hybrid study to allow participants to enroll either virtually (decentralized participants) or at an investigational site (site-based participants).

Decentralized participants are participants who are enrolled virtually and who will not have any assessments performed physically at an investigational site. However, some assessments will require in-person presence of study personnel at the participant's location.

Site-based participants are participants who are enrolled at an investigational site and will have some assessments performed at that site. Note that participants in the EU will only enroll in this study as site-based participants. All site-based participants will still attend 3 decentralized (ie, telemedicine) study visits per the SoA (Table 3). Site-based participants will always have the option to be seen in person at the clinic for these 3 decentralized visits, if needed.

Additionally, all participants in this study will use electronic clinical outcome assessment devices at home. Diary and assessment information will be collected via a smartphone, which will be managed by the participant at home. In addition, BP data will be collected over a 25-hour period using a 24-hour ambulatory BP monitoring device. The BP device will be placed on the participant's arm and initialized in-person by trained site staff and will continue to be worn by participants at home (Section 8.2.1). Site staff will train participants in person on the use of these devices and how to report any AEs (serious and nonserious) that may occur during the study. Participants will also be provided with site and vendor 24-hour contact details for support with any safety or device issues that may arise.

Data collected via these electronic clinical outcome assessment devices will not be accessible to the participant, investigator, or sponsor during collection and will be uploaded to an approved secure portal prior to any review. Details regarding data privacy are provided in the ICF and per Section 10.

4.2. Scientific Rationale for Study Design

A single-arm, open-label, interventional, 2-stage group sequential design has been selected for this study to evaluate BP change in participants switching from twice-nightly high-sodium oxybate (eg, XYREM) to XYWAV. The 2-stage group sequential design is a type of adaptive design in which sample size can be adjusted based on the result of an interim analysis. Given the limited historical information about the 24-hour SBP change related to switching from twice-nightly high-sodium oxybate to XYWAV, this design allows more flexible study conduct and enables a sample size re-estimation based on interim analysis results (Section 9.4 provides additional details about the interim analysis).

The primary endpoint, change from baseline to EOT Visit on the 24-hour average SBP (mm Hg), is a direct measure of a cardiovascular risk factor for multiple morbidities associated with sodium consumption (Sacks, 2001; Lewington, 2002; Cook, 2007; Strazzullo, 2009; Cappuccio, 2011; Whelton, 2012; Mozaffarian, 2014; Smyth, 2016; Kwon, 2017; Fatahi, 2018; Lee, 2018; Cirillo, 2020; Fuchs, 2020; Carey, 2021; FDA, 2021). Ambulatory monitoring of BP over 24 hours is the standard when assessing difference in SBP in clinical studies and more accurately reflects BP changes than single clinical readings. Secondary endpoints of assessing change from the baseline to EOT Visit on the average daytime SBP (mm Hg) and the average nighttime SBP

(mm Hg) were chosen, as average daytime and nighttime changes in SBP may differ due to the clinical status of the study participant, sodium sensitivity, and pharmacodynamics of switching from twice-nightly high-sodium oxybate to XYWAV. [redacted] This criterion was established to ensure that the population most likely to demonstrate an impact on BP benefit from this reduction in sodium is included.

A separate control group is not needed in this study, as a participant's BP would not otherwise be expected to significantly change over the course of a 6-week period without a change in BP medications, diet, or exercise. As noted in Section 5.3, participants should avoid changes in parameters that could affect BP (eg, diet, BP medications, or exercise) during the course of the study.

Offering a decentralized site to allow patients to enroll and participate from their location if they are not near one of the standard research sites will broaden the pool of eligible participants for this study and promote diversity in the study population.

4.3. Justification for Dose

The anticipated XYWAV dosage range in this study (6 to 9 g/night divided into 2 doses) is consistent with the recommend dosage range for both XYWAV and XYREM (twice-nightly high-sodium oxybate) in adult patients with narcolepsy (XYWAV USPI; XYREM USPI). The 1-day switch from twice-nightly high-sodium oxybate (eg, XYREM) to XYWAV on a gram-for-gram basis at the start of the Intervention Period is also consistent with recommendations in the XYWAV USPI (XYWAV USPI).

The inclusion criterion for required high-sodium oxybate at screening (6 to 9 g/night with twice-nightly dosing for ≥ 6 consecutive weeks) was established to ensure adequate exposure to high-sodium oxybate before transition to XYWAV and to confirm participants are on a well-tolerated treatment regimen. Based on published evidence (summarized in Section 2.2), a reduction of between 1000 to 1500 mg/night of sodium (ie, the approximate difference in sodium content between XYREM and XYWAV at 6 to 9 g/night) is hypothesized to result in a clinically relevant decrease in SBP.

4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in the SoA (Section 1.3).

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

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants have a documented diagnosis of Type 1 or Type 2 narcolepsy that meets ICSD-3 or DSM-5 criteria.
3. Participants must have been receiving a total dose of high-sodium oxybate (eg, XYREM) of 6 to 9 g/night (inclusive) with twice-nightly dosing for a minimum of 6 consecutive weeks prior to screening.
4. If currently treated with stimulants and/or alerting agents or other medications known to affect BP, participant must have been taking the same dosing regimen for at least 2 months prior to screening and agree to take the same dose throughout the study.
5. If currently taking stable doses of antihypertensive therapies, participant must maintain these treatments at the same dose throughout the study unless otherwise advised by their medical care provider. Also refer to exclusion criterion 12.

[redacted]

Note: For inclusion criteria 6 and 7, BP measurements will be collected using a device provided by the sponsor as described in Section 8.3.2.1. Participants with resistant hypertension are excluded (refer to exclusion criterion 12).

Sex and Contraceptive/Barrier Requirements

8. Participant is male or female.
   - 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 pregnancy test (serum) as required by local regulations during screening (Section 8.3.5).
- Additional requirements for pregnancy testing during and after study intervention are provided in Section 8.3.5.
- 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 early undetected pregnancy.

Other

9. Willing and possesses the ability to comply with study design schedule and other study requirements (eg, wearing and operating the BP monitoring device as specified, collecting urine as specified, completing required questionnaires, complying with dietary and exercise instructions).
10. Successful completion of 24-hour ambulatory BP measurement within the Screening Period (that includes meeting minimal data quality standards).

Informed Consent

11. Is capable of giving signed 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.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the participant or interfere with study assessments or the ability of the participant to complete the study based on the judgment of the investigator.
2. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic or hospitalized congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, chronic/persistent atrial fibrillation, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or anti-arrhythmic therapy, or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant safety in the study, including screening ECG results.
3. Presence of atrial fibrillation detected on screening ECG.

4. Current or recent (within the past 2 years) diagnosis of a moderate or severe substance use disorder (excluding caffeine) according to DSM-5 criteria. Nicotine use disorder is excluded only if it impacts sleep (ie, a participant who routinely awakens at night to smoke).
5. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.
6. Succinic semi-aldehyde dehydrogenase deficiency by medical history.

Prior/Concurrent Clinical Study Experience

7. Received an investigational drug in the past 30 days or 5 half-lives (whichever is longer) prior to the Screening Period, or plans to use an investigational drug (other than the study drug) during the study.

Diagnostic Assessments

8. Presence of renal impairment with a calculated creatinine clearance < 45 mL/min.
9. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant by the investigator (clinical chemistry). NOTE: clinical labs may be repeated once during the Screening Period.

Other Exclusions

10. Occupation requiring nighttime or variable shift work.
11. Participant was previously eligible for this study but either was terminated early or was discontinued.
12. Participant has resistant hypertension, defined as one of the following:
    a. Controlled BP (ie, SBP < 140 mm Hg and DBP < 90 mm Hg) and treated with 4 or more antihypertensive medications.
    b. Uncontrolled BP (ie, SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) despite concurrent use of 3 or more antihypertensive medications of different classes that include a diuretic.

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 asked to maintain consistent sleeping habits, eating habits, and exercise regimes before and after the switch from twice-nightly high-sodium oxybate to XYWAV, as significant changes in regime may affect BP outcomes.

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 the study intervention.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials 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 failure) may be rescreened once following approval and appropriate documentation by the medical monitor. Rescreening may occur following the resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary when unstable (eg, electrolyte abnormalities). 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

The study intervention planned for use in this study is described in Table 5.

Table 5: Study Treatment/Intervention

Treatment Arm	Intervention/ Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Packaging	Labeling	Storage Conditions
1	JZP258 (XYWAV)	Solution	0.5 g/mL (0.413 g/mL oxybate)	XYWAV will be initiated at the dose equivalent (gram-per-gram) to that for prior high-sodium oxybate[a] twice-nightly regimen (6 to 9 g/night).	Oral	Experimental	Provided centrally by the sponsor	Study intervention medication will be provided in bottles with inserted Press-in Bottle Adapter (and accessories eg, dosing cups and dosing syringe), labeled per country-specific guidelines. All packaging and labeling operations per current Good Manufacturing Practice and local requirements and regulations. Child resistant packaging as required.	Open-label	Store at room temperature between 20°C and 25°C (excursions permitted between 15°C and 30°C).

[a] During the Screening Period, participants will continue to take their own commercial twice-nightly high-sodium oxybate (and any concomitant anticataleptics or stimulants) at the same dose and regimen as prescribed by their healthcare physician prior to enrollment in this study. Participants will use their own supply of twice-nightly high-sodium oxybate (and any other prescribed drugs), which will not be provided separately as part of this study.

The timing for treatment switch from twice-nightly high-sodium oxybate to XYWAV will be scheduled once it has been confirmed that that the ambulatory BP assessment during the Screening Period meets minimum data quality standards. Participants will be provided detailed instructions regarding the exact timing for the treatment switch.

The Intervention Period begins on the day of the treatment switch. That night, participants will initiate the switch from twice-nightly high-sodium oxybate to XYWAV, with an immediate gram-for-gram transition. The switch occurs over 1 night. After the switch to XYWAV, the participant should remain on this same dose of XYWAV for the remainder of the study. Modest dose adjustments are permitted if necessary in the opinion of the investigator (Section 6.6 provides additional details).

Participants will also complete a study intervention dosing diary before and after the switch to XYWAV as specified in the SoA (Section 1.3); additional details are provided in Section 6.5.

6.2. Preparation/Handling/Storage/Accountability

The investigator shall be responsible for maintaining appropriate records and ensuring appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

- Further guidance and information for the final disposition of unused study interventions 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 site staff or designee may supply study intervention.
- The investigator must have country-appropriate controlled substance licensing (eg, Drug Enforcement Administration license for Schedule III drugs) 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 or designee.
- 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

A participant is considered enrolled in the study by providing informed consent/assent 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. Participants who meet all eligibility criteria 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 (sponsor) will provide open-label bottles of XYWAV oral solution 0.5 g/mL for the study.

The participant will self-administer study intervention(s) as directed by study personnel and complete an electronic study intervention dosing diary (refer to Section 8.2.3) as specified in the SoA (Section 1.3). Completeness of the study intervention dosing diary will be discussed and assessed by study personnel. Study personnel will also counsel participants who have not been compliant with dosing and diary completion.

Treatment compliance will be measured (either by study personnel during a site visit or by the participant during a telemedicine visit) and recorded on the drug accountability log by study personnel. A designated staff member will also record the number of bottles and the volume of study intervention dispensed and returned.

Suspected misuse or potential abuse of the study intervention (XYWAV) should be investigated, and participant counseled when there is a discrepancy of ≥ 30 mL between the returned volume and the expected returned volume.

A record of the quantity of study intervention 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 including 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 in the eCRF.

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 per sponsor instructions. If any bottles have not been returned to the site or designee, the reason must be documented. If bottles are not returned at the final visit, the site must document 3 attempts (where possible, 2 telephone calls and a certified letter to the participant) to retrieve the unreturned bottles.

6.6. Dose Modification

Participants will switch from twice-nightly high-sodium oxybate to XYWAV with an immediate gram-for-gram switch (as described in Section 6.1). For participants who, in the opinion of the investigator, require a modest adjustment to their XYWAV (up or down by 1.5 g/night), this adjustment may be made during the Intervention Period, provided the participant's total nightly dose is 6 to 9 g/night (inclusive).

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

At the end of the Intervention Period (after completing an EOT 24-hour BP recording that meets minimum data quality standards [Section 4.1]), participants may transition to commercial XYWAV (in countries where XYWAV has been approved) or another standard of care per 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 reportable experiences. 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

Prohibited and permitted concomitant medications are clarified below.

Prohibited Concomitant Medications

The initiation of new prescriptions of stimulants and/or alerting agents or other medications known to affect BP and/or antihypertensive medications during the study is not allowed (also refer to Section 5.1, inclusion criteria 4 and 5).

Relevant medications known to affect BP and/or hypertensive medications include, but are not limited to, the following:

- Antihypertensives
- Diuretics
- Beta blocking agents
- Calcium channel blockers
- Agents acting on the renin-angiotensin system

The sponsor (or delegate) should be contacted if any new medications of these types are initiated, as this may result in participant discontinuation.

Permitted Concomitant Medications

As specified in the inclusion criteria (Section 5.1) treatment with stimulants and/or alerting agents or other medications known to affect BP (as noted above) is permitted if the participant has taken the same dosing regimen 2 months prior to screening and agrees to take the same dose throughout the study. Modifications in doses of these medicines are permitted if deemed necessary per the investigator's clinical judgment. However, any modifications in doses must be documented, and the sponsor (or delegate) should be contacted to determine whether the participant may remain in 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 E/D Visit in the SoA (Section 1.3). Participants will be asked to complete the Safety Follow-up Visit at least 14 days after the last dose of study intervention.

7.1. 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 at least the second 24-hour BP recording and 24-hour urine sample whenever possible. The SoA (Section 1.3) details the data to be collected at the time of discontinuation of study intervention and follow-up 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 (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 on study intervention
- The participant enrolls in a different clinical study that involves investigational treatment

Discontinuation of specific sites or of the study as a whole are handled as part of Study and Site Start and Closure (Section 10.1.9).

7.1.1. Temporary Discontinuation/Study Intervention Interruption

The decision to interrupt study intervention administration will be at the discretion of the investigator, with input from the medical monitor.

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.

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 study site.

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

- The site 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 (where 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

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Decentralized participants will undergo consent, initial screening, and data collection procedures via online tools using an electronic device (computer or smart phone) with an active internet connection. Completion of some screening assessments will also require in-person presence of study personnel at the participant's location as specified in the SoA (Section 1.3). When the study intervention is prescribed, the principal investigator or a subinvestigator will be present via telemedicine, and study personnel may be present at the participant's location.
- Some assessments will occur as telemedicine visits as specified in the SoA (Section 1.3).
- All screening evaluations must be completed and reviewed 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 repeating the 24-hour BP recording assessment [if needed], returning the BP recording device, 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, per local health authority/ethics requirements.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or medically 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.

This hybrid study will allow participants to enroll either virtually or at a site. Local guidelines and regulations will be followed when using eConsent.

8.1.2. Assignment of Participant Number

Each participant who signs the ICF will be 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.

8.1.3. 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.

8.1.4. Medication Review (Prior and Concomitant Medications)

The investigator or medically qualified designee should review the participant's prior medication use. All medication taken by the participant (ie, prior medications within approximately 2 months before screening and concomitant medications during the study) should be recorded.

8.1.5. 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.

8.1.6. Timing of Study Intervention Dosing

XYWAV should be administered at least 2 hours after eating.

Participants should take each dose of XYWAV while in bed, lie down immediately after dosing, and remain in bed following ingestion of each dose. With twice-nightly dosing, participants may need to set an alarm to awaken for the second dose. If the second dose is missed, that dose should be skipped and XYWAV should not be taken again until the next night. Two XYWAV doses should never be taken at 1 time.

Dosing and dose adjustments are discussed in Section 4.3 and Section 6.6, respectively.

8.2. Efficacy Assessments

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

8.2.1. 24-Hour Blood Pressure Monitoring

Ambulatory BP monitoring is a standard technique in adult antihypertensive studies to assess the magnitude and duration of effect of investigational drugs.

Participants will receive training on the use of the ambulatory BP monitors and will be provided a device for 24-hour home recording of BP.

During the Screening Period, the 24-hour BP recording should not be initiated until all other eligibility criteria have been assessed and are met (however, the BP recording can be initiated prior to obtaining results from the clinical laboratory assessments at screening). This recording at screening must occur no more than 2 weeks prior to the switch from twice-nightly high-sodium oxybate to XYWAV.

The same device should be used to collect each 24-hour BP recording on the participant during the study. Additionally, participants are required to wear the device for approximately 25 hours for each recording to ensure that 24 hours of data are captured.

Participants will be asked to make every effort to capture each 24-hour BP recording beginning at the same start time and on days matched based on activity level. For example, if a participant works from home and exercises on Monday and Wednesday and works out of the office and does not exercise on Tuesday and Thursday, these 2 groups of "routine days" should be matched. In this example, a 24-hour BP recording starting on Monday during the Screening Period should be matched to a 24-hour recording starting on either Monday or Wednesday during the EOT Visit.

The ambulatory BP device will obtain BPs every 20 minutes during the daytime and every 30 minutes during the nighttime over the 24-hour time frame. Once each 24-hour recording is captured, the BP data will be reviewed to confirm adequate collection according to quality control criteria (ie, obtain ≥ 80% of the programmed recordings [a minimum of 50 ambulatory BP measurements] and have ≤ 2 hours contiguous loss of BP readings).

Study personnel (either at the investigational site or at the participant's location) will place the ambulatory BP device on the participant and initiate the 24-hour BP recording. The device can be removed by the participant after completion of the 24-hour BP recording, with detailed instructions from study personnel.

The participant will return to the site with the ambulatory BP device (site-based participants) or study personnel will go to the participant's location (decentralized participants) within 3 days after the conclusion of the 24-hour BP recording (as specified in the SoA [Section 1.3]). At this time, the 24-hour BP data will be assessed for quality criteria. If the 24-hour BP data does not meet the quality criteria, the ambulatory BP device will be placed on the participant to obtain another 24-hour BP recording. Up to 2 additional 24-hour BP recordings may be attempted within 3 days after the prior collection.

8.2.2. 24-Hour Urine Collection

Participants will receive supplies and instructions on the 24-hour urine collection at the time points specified in the SoA (Section 1.3). This collection should occur within 72 hours of the 24-hour BP recording, but this can be extended to 1 week if necessary. The 24-hour urine collection during the Screening Period must occur (but results do not need to be available) prior to the switch from twice-nightly high-sodium oxybate to XYWAV. The total amount of urine sodium excreted over the 24-hour period will be determined based on the sodium concentration and total volume of urine collected over 24 hours.

8.2.3. Sleep and Study Intervention Dosing Diaries

Electronic sleep and study intervention dosing diaries will be completed by the participant daily for approximately 7 days around the time of (and including) each 24-hour BP recording. The sleep diary and the study intervention dosing diary will be completed on the same days. Therefore, the participant will complete a total of approximately 14 days of diary entries, including the days of each 24-hour BP recording.

Site personnel should initialize diaries at each study visit specified in the SoA and review diary data entries during the specified time period (approximately 7 days). Participants who are

missing diary entries should be contacted immediately by site personnel and encouraged to comply with diary entry requirements. Instances of participant noncompliance with diary entry requirements will be recorded as protocol deviations.

Refer to Section 6.5 and the SoA (Section 1.3) for additional details.

8.2.4. Patient Global Impression of Severity

The PGIs is a single-item 7-point Likert-type rating 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: diaphoresis, nocturia, edema, and enuresis.

8.2.5. Patient Global Impression of Change

The PGIc is a 7-point Likert-type scale that is widely used to evaluate efficacy in clinical studies 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: diaphoresis, nocturia, edema, and enuresis.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A physical examination will be performed at Screening to include, at a minimum, upper arm circumference measurement (for the ambulatory BP monitoring cuff) and an abbreviated system review (head, eyes, ears, nose, and throat; chest; heart; lungs; abdomen; and extremities).

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Other Vitals

- BP and pulse measurements should be obtained at the investigational site using the sponsor-provided device (site-based participants) or at the participant's home location with study personnel using the sponsor-provided device (decentralized participants). The same device should be used for each measurement to ensure consistency for a given participant.
- BP and pulse measurements should be preceded by at least 5 minutes of quiet rest (ie, no talking) and obtained while the participant is seated in a quiet setting without distractions (eg, television, cell phones).
- BP and pulse measurements will be obtained using a sponsor-provided OBPM device. Once initiated, this device will start a 5-minute countdown (ie, a rest period), followed by 3 consecutive BP and pulse rate measurements with 1-minute intervals between each measurement. The device will then automatically calculate and record an average for the 3 BP and 3 pulse rate readings (calculated and recorded separately for SBP and DBP).

- At the Screening Visit, BP and pulse measurements should be obtained before blood collection for laboratory tests. BP and pulse may be repeated up to 2 additional times if the investigator considers that the average recorded by the device was unduly influenced by transitory factors (eg, excessive movement or loud noises during measurement). All screening measurements should be reviewed and filed in the source documents. The investigator will select only 1 recording average for purposes of study eligibility.

8.3.2.2. Height and Weight

- Height and weight will be measured and recorded at the time points indicated in the SoA (Section 1.3).
- Weight should be measured at the investigational site (site-based participants) or at home using a digital scale brought to the participant's location by study personnel (decentralized participants). The same device should be used for each measurement to ensure consistency for a given participant.

8.3.3. Electrocardiograms

- A single 12-lead ECG will be obtained as indicated in the SoA (Section 1.3).
- Measurements to be collected will include the following: HR and PR, QRS, and QT intervals.
- The investigator must review the ECG recordings and document this review. All ECG reports must be filed with the source documents.

8.3.4. Clinical Laboratory Assessments

- Appendix 2 provides the list of clinical laboratory tests to be performed, and the SoA (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.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (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), then the results must be recorded.

8.3.5. Pregnancy Testing

- 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 (Section 1.3).

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure (ie, at the EOT or E/D visit, as specified in the SoA [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.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

XYWAV and twice-nightly high-sodium oxybate treatments (eg, XYREM) are considered central nervous system depressants.

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. These participants 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 study intervention.

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 following up all AEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

All AEs and SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

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**.**

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

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 AEs or SAEs after 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 with each participant at subsequent visits/contacts. All SAEs will be followed up 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 suspected unexpected serious adverse reactions 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 followed 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 followed until 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, he or she 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

Pharmacokinetic parameters will not be evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized before the study start date, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of study endpoints.

9.1. Statistical Hypotheses

The primary statistical hypothesis for this study is that after switching from twice-nightly high-sodium oxybate to XYWAV, there will be a statistically significant decrease compared to baseline in 24-hour average SBP after 6 weeks (H_1: $\Delta_{SBP} < 0$).

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

9.1.1. Multiplicity Adjustment

To address the multiplicity issue due to multiple endpoints, a fixed hierarchical testing sequence will be employed. The formal testing procedure will stop when a *P* value exceeds the prespecified significance level. Statistical significance for the primary endpoint will be assessed using O'Brien-Fleming alpha levels of 0.00998 at the interim analysis. If the primary endpoint is met at the interim analysis, study enrollment will end and the primary endpoint will not be tested again (see Section 9.4). If the primary endpoint is not met at the interim analysis, study enrollment will continue and the O'Brien-Fleming alpha level of 0.02194 will be used for the final analysis.

The secondary endpoints will be tested only once – at the interim analysis if the primary endpoint is met at the interim analysis, or at the final analysis if the primary endpoint is not met at the interim analysis but is met at the final analysis. In group sequential designs with hierarchical endpoints, typical alpha recycling methods do not conserve the family-wise error rate, and separate error spending functions for primary and secondary endpoints are suggested (Glimm, 2010). For studies in which O'Brien-Fleming alpha levels are used for testing the primary endpoint, the use of Pocock alpha levels for testing secondary endpoints is recommended (Glimm, 2010). Therefore, statistical significance for each of the secondary endpoints will be assessed using the Pocock alpha level of 0.0168 when assessed at either the interim or final analysis.

Statistical hypotheses to be tested (in sequential order):

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

4. Change in the nighttime average SBP (mm Hg) following 6 weeks of XYWAV treatment after switching from twice-nightly high-sodium oxybate in participants with narcolepsy

Other endpoints will be handled in an exploratory manner and will not be involved in multiplicity adjustment.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

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

9.3. Statistical Analyses

9.3.1. General Considerations

All study data will be summarized using descriptive statistics. Categorical variables (eg, race, ethnicity) will be reported as frequency and percent. Continuous variables will be reported as number of participants, mean, SD, median, minimum, and maximum (eg, age, weight). All summaries, statistical analyses, and individual participant data listings will be completed using SAS software (SAS Institute, Inc.; Cary, NC), version 9.3 or later.

9.3.1.1. Definition of Study Periods for Analysis

Day 1 is defined as the first day of XYWAV use. The Screening Period includes all measurements taken after informed consent is obtained until Day 1. Baseline refers to the most recent observation prior to Day 1. The Intervention Period extends from Day 1 until the EOT Visit or the E/D Visit (whichever is earlier).

Windows for "daytime" and "nighttime" will be designated by the participant per their reported sleep and wake times in the sleep diary on the days that the ambulatory BP monitors are used. Supporting analyses will use fixed time windows for "daytime" and "nighttime" periods as defined in the SAP.

9.3.1.2. Intercurrent Event Strategies

The following intercurrent events may occur during the study:

- Study intervention discontinuation due to AEs, lack of efficacy, or use of other (prohibited) concomitant medications, etc.
- Withdrawal from the study
- Lost to follow-up
- Change in antihypertensive drug use during the Intervention Period

A Treatment Policy strategy will be used for each specified analysis (ie, the data will be collected and analyzed regardless of whether an intercurrent event has occurred). Participants who do not experience certain intercurrent events while on study (eg, change in antihypertensive drug use) will be included in a sensitivity analysis.

If a participant discontinues the study intervention before the scheduled EOT Visit, then the participant's 24-hour ambulatory SBP data will be collected as soon as possible. Missing assessments after discontinuation of study intervention due to an AE, lack of efficacy, or any other reason will not be imputed for the primary analysis.

9.3.1.3. Pooling of Investigational Centers

Data from all investigational centers will be pooled for analyses of all endpoints. Data may also be pooled by region as appropriate for exploratory analyses.

9.3.1.4. Dropouts and Missing Data

Subject to satisfactory data capture throughout the 24-hour period, device-estimated summaries of total, daytime, and nighttime BP measurements will be used where possible. Repeated 24-hour ambulatory measurement is permitted if satisfactory data are not acquired.

All reported data will be included in the summaries without imputation of any missing data.

9.3.2. Primary Endpoint

The primary estimand is described in Section 3. The 24-hour average SBP will be calculated as the average of all ambulatory SBP measurements during the specified 24-hour window.

The primary hypothesis is that the decrease in 24-hour average SBP is statistically significant 6 weeks after switching from twice-nightly high-sodium oxybate to XYWAV.

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

Δ_{SBP} is the difference in the 24-hour average SBP from baseline to EOT, which will be estimated from an analysis of covariance model of the change from baseline as the dependent variable and

mean-centered baseline value as a fixed effect. In addition, 95% confidence intervals will be provided.

Mean centering of baseline values is performed for computational convenience and replaces the observed baseline value in the model (X_i) with ($X_i - X_{mean}$), where X_{mean} is the estimated mean baseline value in the sample (Barnett, 2005). The resultant model is mathematically equivalent to an "observed value" baseline adjustment model, except that the model intercept term is estimated at the sample mean baseline value rather than at zero.

9.3.3. Secondary Endpoints

The secondary estimands are described in Section 3. The 24-hour daytime and nighttime average SBPs will be calculated as the average of all SBP measurements during the daytime and nighttime windows, respectively. Secondary SBP endpoints will be analyzed using the same methods as those used for the primary SBP endpoint.

9.3.4. Exploratory Endpoints

[redacted]

9.3.5. Safety Endpoints

The safety endpoints are described in Section 3. Descriptive analyses of safety variables will be performed using the Safety Set. Adverse events will be mapped to SOC and preferred terms using the MedDRA classification system. No formal statistical testing will be performed.

9.4. Interim Analysis

A 2-stage group sequential design with sample size re-estimation is used for this study. An interim analysis will be performed after 43 participants (75%) have completed the study. This interim analysis will include a binding stopping rule for efficacy if the primary endpoint (specified in Section 3) is met. Using the sample size assumptions described in Section 9.5, the

calculated O'Brien-Fleming alpha level for statistical significance on the primary endpoint is 0.00998 for the interim analysis.

If the primary endpoint does not reach the necessary significance level for early termination at the interim analysis, study enrollment will continue and the final sample size will be adaptively determined using a "promising zone" approach (Mehta, 2011). Based on the observed effect size at the interim analysis, the conditional power (ie, probability of reaching statistical significance at the final analysis given the data obtained at the interim) for the primary endpoint will be calculated. Because the Type I error probability is not inflated when using conditional power and the promising zone methodology used in this study to determine the situations in which the sample size can be increased (Mehta, 2011), no further adjustment to the O'Brien-Fleming boundaries (described in Section 9.1.1) is required for the final analysis.

The conditional power is calculated as follows (Mehta, 2011, equation 6):

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

Where:

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

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

n_2 = planned sample size at final analysis (ie, n_2 = 57)

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

z_α = the standard normal value for a type I error rate of α; ie, Φ(1 – 0.025) = 1.95996

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

Based on the calculated conditional power, one of the following 3 actions will be taken:

1. "Favorable zone": If conditional power ≥ 90%, continue enrolling participants until the prespecified target sample size (N = 57).
2. "Promising zone": If 40% ≤ conditional power < 90%, increase the target sample size to $(43 + \tilde{n}_2')$, up to a maximum of 77 completers.
3. "Unfavorable zone": If conditional power < 40%, continue enrolling participants until the prespecified target sample size (N = 57).

When the conditional power falls into the "promising zone", the additional sample size required is calculated as follows (Mehta, 2011, equation 9):

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

Where:

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

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

z_α = the standard normal value for a type I error rate of α; ie, Φ(1 – 0.025) = 1.95996

z_β = the standard normal value for a type II error rate of β; ie, Φ(1 – 0.10) = 1.28155

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

The favorable zone threshold was set to the target study power (90%; Mehta, 2011). Based on the study parameters, the unfavorable zone threshold was determined to be approximately 40% (Mehta, 2011, equations 10 to 12).

Enrollment will continue while the interim analysis is being performed. To mitigate the risk of enrolling more participants than needed (ie, "overruns"), the interim analysis will be conducted using the primary endpoint only, which will shorten the time needed to perform the analysis. However, all participants meeting analysis set criteria will be included in the final study report, regardless of the adaptive sample size target.

9.5. Sample Size Determination

The sample size is dependent upon the results of the planned interim analysis (refer to Section 9.4). The sample size also accounts for a 60% screen failure rate after enrollment (ie, signing the ICF) during the Screening Period and assumes a 15% discontinuation/withdrawal rate during the Intervention Period. Based on these assumptions, approximately 170 (up to approximately 230) study participants will enroll to enable a minimum of 67 (up to approximately 91) to initiate the study intervention (ie, switch to XYWAV) and to capture complete data (both during the Screening Period and at the EOT Visit) for a minimum of 57 participants (up to approximately 77).

There are no historical data on 24-hour average BP changes in participants switching from twice-nightly high-sodium oxybate to XYWAV. Given the limited information, data from other studies with drugs similar to oxybate were leveraged to inform the design of this study. It was determined that an effect size of 3.0 or 3.5 with a SD range from 7.0 to 8.0 will be considered for power and sample size calculations. Sample sizes for different scenarios (different effect size and SD) were calculated (Table 6). Power calculations were performed assuming a 1-sided Type 1 error rate of 0.025.

Table 6: Power and Sample Size Calculations

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

A preselected target sample size of 57 completers (n_0 = 57) will provide 90% power to detect a difference of 3.5 points in means for the change from the baseline to the EOT Visit (after 6

weeks of treatment on XYWAV) in 24-hour average SBP when switching from twice-nightly high-sodium oxybate to XYWAV, assuming an SD of 8.0 points.

After 75% of participants have completed the study, an interim analysis will be conducted. If the study does not stop early for efficacy, conditional power for the primary endpoint will be calculated, and the adaptive sample size target may be increased up to a maximum of 77 participants (refer to Section 9.4).

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 with 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 devices and systems involved in data collection for this study are in compliance with EMA/226170/2021.
- Decentralized aspects of this study, where applicable, are in compliance with local regulations, including the EU Recommendation Paper on Decentralized Elements in Clinical Trials - Version 01, 13 Dec 2022.
  - Site staff will train the participant on the use of the study devices, including how to report any AEs (serious and nonserious) that may occur during the study, at their first clinic visit, and the participant will be given additional reminders during the course of the study.
  - The participant will be provided with site and vendor 24-hour contact details for support with any safety or device issues that may arise.
- 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 (if applicable), 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 GDPR requirements (where applicable), and the IRB/IEC or study center.
- 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.
- This hybrid study will allow participants to enroll either virtually or at a site. Local guidelines and regulations will be followed when using eConsent.

10.1.4. Data Protection

- Appropriate steps will be taken to protect participant's 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 will be informed of data privacy regarding the use of electronic clinical outcome assessment devices in the ICF.
- 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. Committee 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 investigator's study site 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

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APPENDIX 2. CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory, unless otherwise noted. The timing and frequency of these tests are specified in the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 Laboratory Tests

Laboratory Tests	**Parameters**			
Clinical Chemistry[a]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Creatinine clearance (eGFR)	Calcium	Alkaline phosphatase[b]	
24-Hour Urine	Urine sodium	Urine potassium	Urine creatinine	Microalbumin
Pregnancy Testing	Highly sensitive serum pregnancy test (as needed for women of childbearing potential) at screening. Urine pregnancy (office- or home-based dipstick) test (as needed for women of childbearing potential) at subsequent visits			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

[a] All events of ALT or AST 3 × ULN and total bilirubin 2 × ULN (>35% direct bilirubin) or ALT or AST 3 × 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.

Investigators must document their review of each laboratory safety report.

APPENDIX 3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• 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
• 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 that are noted by the participant in their diary.

Events Meeting the AE Definition
• 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. • 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. Overdose per se will not be reported as an AE/SAE unless it is an

Events Meeting the AE Definition
intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• 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
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.
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. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

An SAE is defined as any untoward medical occurrence SAE that, at any dose:

- 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

Other situations:

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.

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.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, the 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

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
    - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental 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.

Assessment of Intensity

- 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 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.

Follow-up of AEs and SAEs

- 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 SAEs/OREs/ Pregnancy Reports

Reporting to Sponsor or Designee Through Electronic Data Collection Tool (via RAVE Safety Gateway)
• 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 or ORE/pregnancy report from a study participant or receives updated data on a previously reported SAE or ORE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or ORE/pregnancy report paper form. • Contacts for SAE and ORE 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
• The primary mechanism for reporting an SAE or 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 paper SAE form or ORE/pregnancy paper form may be sent by mail or courier service to the sponsor or designee. • Contacts for SAE 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
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]

• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *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.* 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
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Intravaginal o Transdermal o Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o Oral o Injectable
• Sexual abstinence *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.*

[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 Clinical Trial Facilitation Group 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 03 (Date: 14 Mar 2024)

This amendment was considered to be nonsubstantial 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, because it neither significantly impacted the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for Amendment 03 was to clarify aspects of the interim analysis. A description of changes is provided below. Minor editorial changes have not been summarized in the table.

Section # and Name	Description of Change	Brief Rationale
• 9.1.1 Multiplicity Adjustment • 9.4 Interim Analysis	Provided additional background on the planned interim analysis.	Clarifications.
• Sponsor Signatory	The sponsor signatory was updated.	Update.

Amendment 02 (Date: 06 Dec 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 overall rationale for Amendment 02 was to incorporate clarifying content from an EU-specific amendment into a global protocol. In addition, the analysis plan was updated to bring the Type I error rate in line with the nominal value. A description of changes is provided below. Minor editorial changes have not been summarized in the table.

Section # and Name	Description of Change	Brief Rationale
• Synopsis • Schema • 4.1. Overall Design • 4.2. Scientific Rationale for Study Design • 6.9. Concomitant Therapy • 9.3.1.1. Definitions of Study Periods for Analysis	Content from Appendix 5 (Country-Specific Requirements) of Amendment 01/EU 1 was incorporated into the body of the global protocol.	Clarifications.

Section # and Name	Description of Change	Brief Rationale
• 9.3.2. Primary Endpoint • 9.3.4. Exploratory Endpoints • 9.5. Sample Size Determination • 10.1.1. Regulatory and Ethical Considerations • 10.1.4. Data Protection • Appendix 1. References		
• 9.1.1. Multiplicity Adjustment • 9.4. Interim Analysis • 9.5 Sample Size Determination • Appendix 1. References	The prespecified alpha levels were modified to bring the Type I error rate in line with the nominal value.	Correction; results from simulation analyses suggested the Type I error rate was higher than expected.

Amendment 01/EU 01 (Date: 06 Nov 2023)

This EU-specific amendment is considered to be nonsubstantial 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 overall rationale for the changes implemented in Amendment 01/EU 1 was to provide clarification in response to comments from EU member states via CTIS. Minor editorial changes have not been summarized. A description of changes is provided below.

Section # and Name	Description of Change	Brief Rationale
Appendix 5. Country-Specific Requirements Note: Protocol Amendment History was moved to Appendix 6.	A new appendix was added with EU-specific clarifications for the following sections of the protocol: • Section 1.1. Synopsis • Section 1.2 Schema • Section 4.1. Overall Design • Section 4.2. Scientific Rationale for Study Design • Section 6.9. Concomitant Therapy • Section 9. Statistical Considerations • Section 10.1.1. Regulatory and Ethical Considerations • Section 10.1.4. Data Protection • Appendix 1. References	For clarification in response to CTIS comments.

Amendment 01 (Date: 29 Mar 2023)

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment 01 was to change the phase of the study stated in the protocol from Phase 4 to Phase 3/Phase 4. The protocol was amended to clarify that in regions where the study drug XYWAV follows approved label, the protocol is a Phase 4 interventional study, and in regions where XYWAV does not follow approved label, the protocol is a Phase 3 study. Minor editorial changes for clarity are not included in the table below.

Section # and Name	Description of Change	Brief Rationale
Title Page, Synopsis and Section 4.1 Overall Study Design	Changed the phase in the protocol from Phase 4 to Phase 3/Phase 4 and added an explanation of the phase difference in regions where XYWAV follows approved label.	The purpose of this change is to clarify the phase of this study protocol for regions where XYWAV follows approved label.

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 US FDA regulations relating to GCP 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 ICH 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}

[redacted] 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 JZP258-406-04 Protocol Amendment
VV-CLIN-025140

Approval Task - Approval of Document Signing Verdict/Reason: I Approved This Document	[redacted] Medical Affairs 17-May-2024 18:36:39 GMT+0000

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