TITLE PAGE

Protocol Title:

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

Protocol Number: JZP258-401-00

Amendment Number: N/A (Original Protocol)

Compound: JZP-258 (XYWAV)

Brief Title: An Interventional Safety Switch Study (IS3) of XYWAV in Narcolepsy

Study Phase: 4

Sponsor Name: Jazz Pharmaceuticals Inc.

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

Regulatory Agency Identifier Number(s): [redacted]

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Brief Title:

An Interventional Safety Switch Study (IS3) of XYWAV in Narcolepsy

Rationale:

XYWAV has been approved in the United States (US) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (XYWAV US Prescribing Information [USPI] 2020).

The rationale for the interventional, open-label, single-arm design of Study JZP258-401 is to evaluate the clinical experience in participants with narcolepsy transitioning treatment from Xyrem to XYWAV, through achieving the following key objectives:

- Provide descriptive evidence of safety, tolerability, effectiveness and treatment optimization during switching of Xyrem-stable participants to XYWAV
- Demonstrate that a range of effectively treated Xyrem participants can be effectively switched to XYWAV
- Explore dosing and administration instructions to support an initial conversion to XYWAV on a gram-per-gram basis as Xyrem. Once the investigator determines that a stable dose and regimen is achieved, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator.
- Expand the body of knowledge of clinical experience of participants switching from Xyrem to XYWAV with regard to safety, tolerability, effectiveness and treatment optimization for XYWAV

The study design will enable weekly assessments of participants to gain an understanding of participant experience during switching from Xyrem to XYWAV. A repeated (weekly) visit design has been utilized to provide frequent data points as participants proceed through treatment conversion and optimization process with XYWAV.

An extended 2-week ‘Baseline’ period during which participants will remain on their currently prescribed, baseline Xyrem dose and regimen has been included to collect additional baseline data. The open-label design of this study is deemed appropriate for this purpose, as the efficacy of XYWAV was previously established in a controlled, phase 3 clinical study (15-006) supporting the approval of XYWAV for the narcolepsy indication.

To build on the existing knowledge base of XYWAV, investigators will instruct participants to initially transition from Xyrem to XYWAV at the same dose and regimen as Xyrem. Once the investigator determines that a stable dose and regimen of XYWAV is achieved, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator, as described in Section 8.1.6.

Additionally, an optional interim analysis may be conducted without pause in enrollment, as described in Section 9.5.

Objectives and Endpoints:

Table 1 Objectives and Endpoints

Objectives	**Key Endpoints**
To describe the clinical experience of participants switching from Xyrem to XYWAV for the treatment of narcolepsy with or without cataplexy in terms of safety, tolerability, effectiveness, and treatment optimization.	• Adverse Events and Serious Adverse Events • Change in the Nausea Visual Analog Scale • Change in weekly rate of cataplexy attacks (for Narcolepsy Type 1) • Change in Epworth Sleepiness Scale to assess excessive daytime sleepiness • Participant Global Impression of Change • Time to optimized dose and regimen • Number of changes from first dose and regimen to optimized dose and regimen • Number of participants dosing fasted versus dosing without consideration of food • Timing and characterization of meals relative to dosing
Exploratory Objectives	**Exploratory Endpoints**
To describe the ease of conversion and participant preference of XYWAV in participants with narcolepsy with or without cataplexy	• Ease of Switching Medications Scale • Forced Preference Questionnaire

Overall Design:

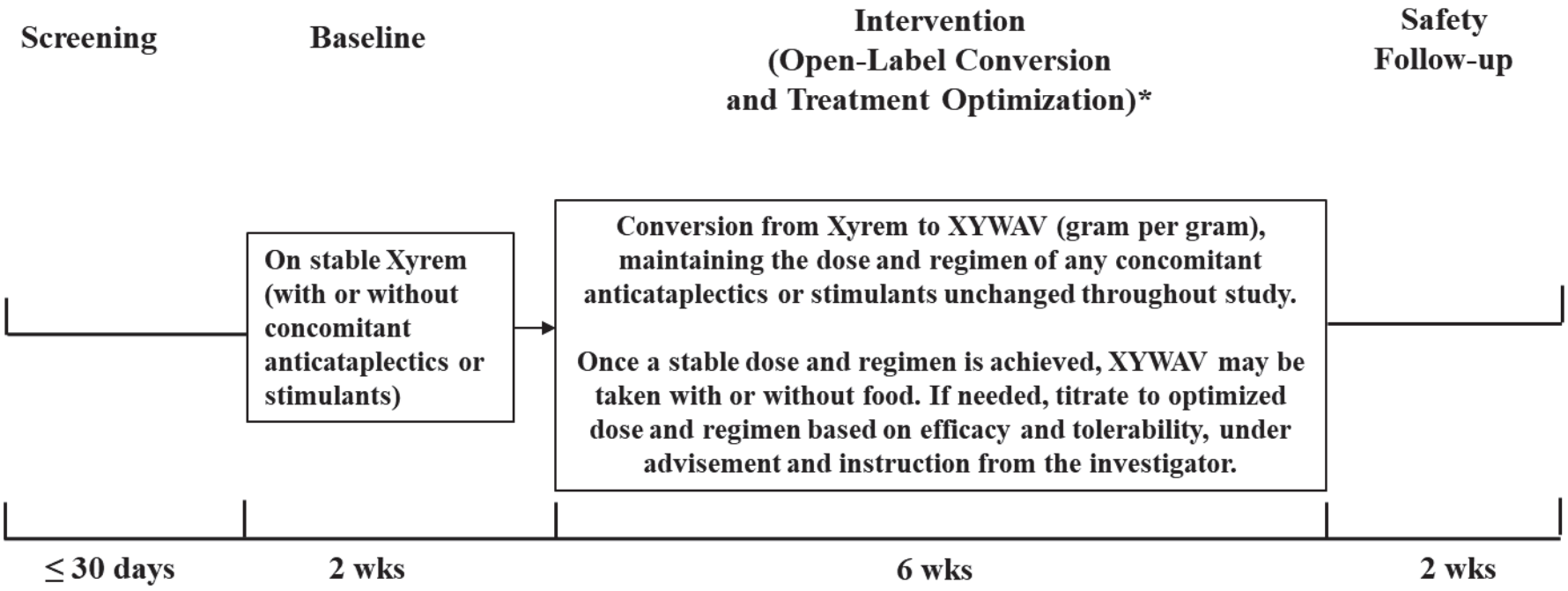
Study JZP258-401 is a multi-center, open-label, single-arm, phase 4 clinical trial designed to describe the clinical experience of participants switching from Xyrem to XYWAV in terms of safety, tolerability, effectiveness, and optimization of treatment.

Table 2 Overall Study Design

Overall Design	
Study Phase	Phase 4
Clinical Indication	Narcolepsy
Study Type	Interventional
Type of Design	Open-label, single-arm, multicenter study for conversion and treatment optimization from Xyrem to XYWAV
Type of Control	None
Study Blinding	Open-label
Population	Participants with narcolepsy
Number of Participants	An estimated total of 100 participants will be enrolled
Duration of Participants	The study starts from the time participants sign the informed consent form (ICF) through the end of the study procedures/contact. Estimated study duration spanning from first participant in (FPI) to last participant out (LPO) / last follow-up visit is 17 months. For each participant the estimated duration from consent to completion is 14 weeks. The study is comprised of the following 4 distinct periods: • Screening period (up to 30 days) • Baseline (Xyrem-stable dose and regimen) period (2 weeks) • Intervention (Open-label Conversion and Treatment Optimization) period (6 weeks) • Safety Follow-up period (2 weeks)
Number of Treatment Arms	1
Treatment Groups	XYWAV (XYWAV started on the same dose [gm-per-gm] and regimen as Xyrem and subsequently stabilized and optimized to an effective dose [up to a maximum nightly dose of 9 grams] and regimen, at investigator's discretion)
Data Monitoring Committee	A data monitoring committee is not planned for this study.

1.2. Schema

Figure 1 Schematic Representation of Overall Design of Study JZP258-401



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

Abbreviations: EDS = excessive daytime sleepiness; wks = weeks

1.3. Schedule of Activities (SoA)

Table 3 Schedule of Assessments

Procedure	Screening Period (Up to 30 days before Day 1)	Baseline Period	Intervention Period (Open Label Conversion and Treatment Optimization Period)				Early Discontinuation (E/D)[3]	Safety Follow-up Period
		Xyrem-Stable Dose and Regimen	Conversion from Xyrem to XYWAV[1]	Treatment Optimization on XYWAV[2]		End of Treatment (ET)[3]		
Visit (V) Number[4]	**V1**	**V2**	**V3**	**V4 Clinic Visit**	**V5, V6 Phone Call**	**V7 Clinic Visit**	**V8**	
Visit Window +/- Day or End of Week (W)	**Day -30 to -1**	**Day 1**	**Day 15 + 1 day**	**W3 +3 days**	**W4, W5 +3 days**	**W6 +3 days**	**W8 +3 days**	**W10 +3 days**
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical History	X	X						
Physical Examination	X							
Vital Signs (BP, HR, body temperature, RR)	X	X	X	X		X	X	X	X
Comprehensive metabolic panel, hematology, UA, TSH	X							
Urine Drug Screen	X	X	X	X		X	X	X	
Alcohol Screen	X	X	X	X		X	X	X	
Serum Pregnancy Test	X							

Procedure	**Screening Period (Up to 30 days before Day 1)**	**Baseline Period**	**Intervention Period (Open Label Conversion and Treatment Optimization Period)**				**Early Discontinuation (E/D)[3]**	**Safety Follow-up Period**
		Xyrem-Stable Dose and Regimen	**Conversion from Xyrem to XYWAV[1]**	**Treatment Optimization on XYWAV[2]**			**End of Treatment (ET)[3]**	
Visit (V) Number[4]	**V1**	**V2**	**V3**	**V4 Clinic Visit**	**V5, V6 Phone Call**	**V7 Clinic Visit**	**V8**	
Visit Window +/- Day or End of Week (W)	**Day -30 to -1**	**Day 1**	**Day 15 + 1 day**	**W3 +3 days**	**W4, W5 +3 days**	**W6 +3 days**	**W8 +3 days**	**W10 +3 days**
Electrocardiogram	X							
Cataplexy Frequency Diary; Assess control of cataplexy (Appendix 5)		X[5]	X	X	X	X	X	X
Review/discuss participant diaries for completeness		X	X	X	X	X	X	X
Nausea Visual Analog Scale (Appendix 6)			X[6]				X[6]	X[6]
Epworth Sleepiness Scale; Assess control of EDS		X					X	X
Forced Preference Questionnaire (Appendix 9)							X	X
Ease of Switching Medications Scale (Appendix 8)							X	X

Procedure	**Screening Period (Up to 30 days before Day 1)**	**Baseline Period**	**Intervention Period (Open Label Conversion and Treatment Optimization Period)**				**Early Discontinuation (E/D)[3]**	**Safety Follow-up Period**
		Xyrem-Stable Dose and Regimen	**Conversion from Xyrem to XYWAV[1]**	**Treatment Optimization on XYWAV[2]**			**End of Treatment (ET)[3]**	
Visit (V) Number[4]	**V1**	**V2**	**V3**	**V4 Clinic Visit**	**V5, V6 Phone Call**	**V7 Clinic Visit**	**V8**	
Visit Window +/- Day or End of Week (W)	**Day -30 to -1**	**Day 1**	**Day 15 + 1 day**	**W3 +3 days**	**W4, W5 +3 days**	**W6 +3 days**	**W8 +3 days**	**W10 +3 days**
Participant Global Impression of Change							X	X	
Columbia-Suicide Severity Rating Scale Screening (Baseline version)	X								
Participant Health Questionnaire-9	X								
Adverse Events and Serious Adverse Events Reporting (Appendix 7)	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Food and Drug Dosing Diary (Appendix 4) Assess diary for completeness and compliance after start of dosing		X[5]	X	X	X	X	X	X	

Procedure	Screening Period (Up to 30 days before Day 1)	Baseline Period	Intervention Period (Open Label Conversion and Treatment Optimization Period)					Early Discontinuation (E/D)[3]	Safety Follow-up Period
		Xyrem-Stable Dose and Regimen	Conversion from Xyrem to XYWAV[1]	Treatment Optimization on XYWAV[2]			End of Treatment (ET)[3]		
Visit (V) Number[4]	**V1**	**V2**	**V3**	**V4 Clinic Visit**	**V5, V6 Phone Call**	**V7 Clinic Visit**	**V8**		
Visit Window +/- Day or End of Week (W)	**Day -30 to -1**	**Day 1**	**Day 15 + 1 day**	**W3 +3 days**	**W4, W5 +3 days**	**W6 +3 days**	**W8 +3 days**		**W10 +3 days**
Dispense study drug			X			X			
Collect study drug, measure compliance						X	X	X	

Abbreviations: BP = blood pressure; EDS = excessive daytime sleepiness; HR = heart rate; RR = respiratory rate; TSH = thyroid-stimulating hormone; UA = urinalysis

1. All participants will begin XYWAV treatment at the beginning of the Intervention (Open-label Conversion and Treatment Optimization) period, starting the night of Visit 3/Day 15 and continue through to the End of Treatment (ET) (Visit 8) or Early Discontinuation (E/D), as applicable.
2. Participants must be on an optimized dose of XYWAV for at least the final 2 weeks of the Intervention Period.
3. Following ET (Visit 8) or E/D, investigators will determine the appropriate course of care with the participant, with the option to resume medications that were discontinued prior to or during study participation.
4. The investigator may have the participant attend an unscheduled visit at any time during the study, if deemed necessary.
5. The participant is expected to start indicated diary completion on the morning after the participant enters the Baseline period (Day 1).
6. NVAS will be captured daily during the last 7 days of the Baseline (Xyrem-stable dose and regimen) period and the last 7 days of the Intervention period (on XYWAV) prior to the ET visit, or prior to the E/D visit, if possible.

2. INTRODUCTION

XYWAV (JZP-258) oral solution has been developed by Jazz Pharmaceuticals (Jazz) as an alternative, low-sodium formulation for Xyrem (sodium oxybate) and was recently approved in the US for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy (XYWAV USPI 2020).

Xyrem oral solution (0.5 g/mL) 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 2020). Xyrem is also approved in Canada for the treatment of cataplexy in patients with narcolepsy (Xyrem Canadian Product Monograph 2014), and in the European Union (EU) (Xyrem EU Summary of Product Characteristics [SmPC] 2015) for the treatment of narcolepsy with cataplexy in adult patients.

XYWAV and Xyrem contain the same active moiety, which is the endogenous neuropeptide, gamma hydroxybutyrate (GHB) or oxybate, at the same concentration. However, compared to the sodium oxybate composition of Xyrem, the unique mixed salt formulation of XYWAV (comprised of calcium, potassium, magnesium, and sodium salts of oxybate) results in 92% less sodium – or approximately 1,000 to 1,500 mg/night – than Xyrem, at the recommended dosage range of 6 to 9 grams.

While Xyrem has been proven safe and effective 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 (AASM) (Morgenthaler 2007), the current formulation of Xyrem (sodium oxybate) imposes a significant sodium burden to an individual's diet. The American Heart Association (AHA) and the Food and Drug Administration (FDA) recommend no more than 2300 mg of sodium intake per day, with an ideal limit of no more than 1,500 mg per day for most adults (AHA 2018; FDA 2016). Additionally, an increased risk of cardiovascular disease has been causally associated with high levels of sodium intake (FDA 2016; National Academies of Sciences, Engineering, and Medicine 2019; Whelton 2012). Administration of the maximum recommended daily dose of Xyrem (9 grams/day), results in an intake of 1.64 grams sodium/day, akin to 109% of the ideal recommended dietary allowance of sodium per day (CDC 2010).

Excess sodium intake is correlated with increases in blood pressure (BP), hypertension, stroke, and other cardiovascular disease (Mente 2014, Gardner 2012, Institute of Medicine [IOM] 2005). Epidemiological studies indicate an increased risk of morbidity and mortality from cardiovascular diseases, including coronary heart disease and stroke, with increased sodium intake (EFSA 2006). The current USPI for Xyrem oral solution includes a warning to monitor patients who are sensitive to salt intake (eg, those with heart failure, hypertension, or impaired renal function), conditions that are common in the narcolepsy population (Ohayon 2013; EFSA 2006).

With the goal of establishing a new standard of care for participants with narcolepsy, the low-sodium formulation of XYWAV has been designed to preserve the same concentration of oxybate as that in Xyrem, but with a significantly reduced sodium load that does not warrant warnings about sodium content. The sodium contribution of XYWAV is approximately 10% of the ideal RDA (compared to sodium levels of 109% RDA in Xyrem). Thus, XYWAV provides the same therapeutic benefits of Xyrem while offering an improved safety profile owing to the reduced sodium content, particularly for participants with sodium-sensitive conditions and those concerned about limiting their daily sodium intake.

The therapeutic efficacy and safety of XYWAV has been demonstrated in a global phase 3 double-blinded, placebo-controlled, randomized-withdrawal, multicenter clinical trial (Study 15-006, NCT03030599), including a 24-week open-label extension (OLE) period, in patients with narcolepsy

(XYWAV USPI 2020, Thorpy 2020). In Study 15-006, which enrolled 201 patients and randomized 134 patients, XYWAV demonstrated significant differences ($p<0.0001$) in the weekly number of cataplexy attacks and Epworth Sleepiness Scale (ESS) scores (a measure of EDS) compared to placebo. Additionally, the safety profile of XYWAV was consistent with that expected for oxybate.

This current study (JZP258-401) is a multi-center, open-label, single-arm, phase 4 trial that seeks to build upon the demonstrated benefits of XYWAV and provide further descriptive evidence of safety, effectiveness, tolerability and treatment optimization in participants switching from Xyrem to XYWAV. The study will include comparative assessments related to treatment-based and exposure-related adverse events (AE), tolerability, and therapeutic effectiveness of disease control between Xyrem and XYWAV. Participants will be switched from Xyrem to XYWAV at the same dose and regimen as Xyrem. Once the investigator determines that a stable dose and regimen of XYWAV is achieved, participants will be allowed to dose with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator.

Success in this study will be indicated by seamless switching of the majority of participants from Xyrem to XYWAV, with little or no changes in dose strength or regimen. Additionally, evidence will be provided to support participant preference for XYWAV based on its lower level of sodium, potentially improved tolerability profile, a safety profile typical of oxybate, and similar disease control as participant's current Xyrem dose and regimen. Collectively, these data are expected to expand the knowledgebase of clinical experience in the population of participants with narcolepsy transitioning from Xyrem to XYWAV.

2.1. Study Rationale

Study JZP258-401 is an open-label, single arm, phase 4 interventional trial designed to provide descriptive evidence on the safety, tolerability, effectiveness and optimization of treatment associated with the switching of Xyrem-stable participants with narcolepsy to XYWAV.

The objectives of the study are to delineate the overall clinical experience associated with treatment switching from Xyrem to XYWAV, and evaluate if conversion to XYWAV can be performed with relative ease and rapidity, and with minimal adjustment of dose and regimen. Additionally, the study will collect evidence on whether in comparison with Xyrem, XYWAV offers greater flexibility in dosing with regard to food and improved tolerability for nausea. This study will also evaluate patient preference for the low-sodium formulation of XYWAV relative to that of Xyrem.

2.2. Background

Narcolepsy is a severe sleep disorder involving the dysregulation of sleep-wake cycles that is primarily characterized by EDS and manifested with or without features of rapid-eye movement (REM) sleep dissociation (eg, cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis), and disrupted nighttime sleep (AASM 2014; Boscolo-Berto 2012, Dauvilliers 2007; Dauvilliers 2012; Nishino 2007; Ruoff and Rye 2016; Thorpy 2014). Narcolepsy is a chronic neurologic condition with no cure identified to date and a demonstrated burden of illness that can have far-reaching impacts on an individual's health over time (Ahmed 2016; Plazzi 2018; AASM 2014). 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 and Hirschkowitz 2010).

The precise mechanism of action of sodium oxybate in narcolepsy is not known. It is hypothesized that its effects on cataplexy and EDS are mediated through neuropharmacologic, B-subtype of the gamma-aminobutyric acid receptor (GABABR)-mediated actions on noradrenergic and dopaminergic neurons, as well as on thalamocortical neurons (Xyrem USPI 2020; Pardi and Black 2006; Mathivet 1997, Lingenhoehl 1999; Snead 2000). Evidence from clinical trials have shown that sodium oxybate

increases delta (slow-wave or restorative) sleep and improves sleep continuity. Other effects include increases in brain acetylcholine, and depression of glucose utilization, but not oxygen consumption, in the brain (Pardi and Black 2006). XYWAV was developed as a mixture of 4 oxybate salts to substantially lower sodium content relative to the current Xyrem formulation.

The therapeutic benefits and safety of oxybate for treatment of cataplexy and EDS in narcolepsy have been demonstrated through extensive clinical trials and post-marketing experience using Xyrem, and in recent clinical trials with XYWAV. Specifically, the efficacy and safety of XYWAV has been demonstrated in a randomized, controlled clinical trial (Study 15-006) which resulted in the approval of XYWAV for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy (XYWAV USPI 2020). In addition, the magnitude of the food effects appears to be lower with XYWAV (compared to Xyrem); however, dosing instructions require the first nightly dosing to occur at least 2 hours after the last meal. The present study is conducted to provide additional open-label evidence to support that participants on current Xyrem therapy can effectively and efficiently convert from Xyrem to XYWAV in a safe manner, with minimal tolerability challenges and maintain effective disease control. A detailed description of the chemistry, pharmacology, efficacy, and safety of XYWAV is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

A summary of the benefit-risk assessment for conducting Study JZP258-401 is provided in the subsections below.

2.3.1. Risk Assessment

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

- Participants may experience worsening of disease control with XYWAV compared to Xyrem
- Participants may experience reduced tolerability for XYWAV compared with Xyrem
- Procedural risks during screening, including risks and/or discomfort associated with clinical laboratory assessments and electrocardiography.

2.3.2. Benefit Assessment

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

- Participants may experience improved disease control with XYWAV compared to Xyrem
- Participants may experience improved tolerability for XYWAV relative to Xyrem
- Participants may experience improved dosing flexibility of XYWAV with regard to timing of food intake
- Participants switching from Xyrem to XYWAV may have reduced medical risks associated with high levels of sodium consumption

2.3.3. Overall Benefit : Risk Conclusion

Benefits to participants include receiving therapy that may potentially alleviate symptoms of narcolepsy, while contributing to the knowledge base and clinical experience of new therapeutics for narcolepsy. Additionally, participants may experience health benefits from receiving comprehensive physical examinations (PE), clinical monitoring and laboratory testing. Risks to participants include those associated with administration of XYWAV and are expected to be similar to those seen in prior clinical studies, as detailed in the IB. Additional risks include the potential need to discontinue any prohibited medications, and potential risks related to study procedures.

3. OBJECTIVES AND ENDPOINTS

Objectives	Key Endpoints
To describe the clinical experience of participants switching from Xyrem to XYWAV for the treatment of narcolepsy with or without cataplexy in terms of safety, tolerability, effectiveness, and treatment optimization.	• Adverse Events and Serious Adverse Events • Change in the Nausea Visual Analog Scale • Change in weekly rate of cataplexy attacks (for Narcolepsy Type 1) • Change in Epworth Sleepiness Scale to assess excessive daytime sleepiness • Participant Global Impression of Change • Time to optimized dose and regimen • Number of changes from first dose and regimen to optimized dose and regimen • Number of participants dosing fasted versus dosing without consideration of food • Timing and characterization of meals relative to dosing
Exploratory Objectives	**Exploratory Endpoints**
To describe the ease of conversion and participant preference of XYWAV in participants with narcolepsy with or without cataplexy	• Ease of Switching Medications Scale • Forced Preference Questionnaire

4. STUDY DESIGN

Study JZP258-401 is an open-label, single-arm, phase 4 clinical study designed to describe the overall clinical experience in participants with narcolepsy transitioning treatment from Xyrem to XYWAV.

4.1. Overall Design

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

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

An estimated total of 100 eligible participants with narcolepsy will be enrolled into this single-arm study. The total duration of the study is expected to be approximately 17 months, with duration of individual subject participation around 3 to 3.5 months. The study comprises the following phases:

Screening Period (Up to 30 days)

To be eligible for the study, all participants must have been titrated to a tolerable and effective dose and regimen of Xyrem (with or without any concomitant anticataplectics or stimulants), which shall have remained stable for ≥ 2 months prior to entry into study. During the initial Screening period of up to 30 days, all participants will be evaluated for eligibility based on screening assessments (Section 1.3), with the option to rescreen once (Section 5.4).

Baseline Period (2 weeks)

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

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

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

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

Safety Follow-up Period

Following the Intervention period, participants will return for a Safety Follow-up visit 2 weeks after the End of Treatment (ET) or Early Discontinuation (E/D) (Section 1.3). Following the ET or E/D, including during the Safety Follow-up period, it is understood and expected that investigators will determine the appropriate course of care with the participant, and may resume any prescribed medications that were discontinued prior or during the study. There is no plan to monitor participants beyond the 2-week Safety Follow-up period.

Assessments of all study endpoints (as listed in Section 3) will be summarized descriptively. Formal hypothesis testing will not be performed.

An optional interim analysis may be conducted, without pause in enrollment, as described in Section 9.5. A Data Monitoring Committee is not planned for this study.

4.2. Scientific Rationale for Study Design

The open-label design of Study JZP258-401 is intended to enable descriptive assessments of safety, tolerability, effectiveness and optimization of treatment associated with switching of Xyrem-stable participants to XYWAV.

An estimated total of 100 participants are expected to be enrolled in this study to achieve the study objectives, and further expand the current database of known participants transitioning to XYWAV. In the previous phase-3 pivotal trial (Study 15-006) for XYWAV in patients with narcolepsy, a set of 75 patients switching to XYWAV were sampled. This current study will add another estimated 100 cases, thus expanding the size of the XYWAV-conversion participant database.

Repeated (weekly) visits have been incorporated as part of the study schedule to capture frequent data points as participants proceed through the treatment conversion and optimization process with XYWAV. The frequency and schedule of visits is designed to maximize participant-investigator interaction at critical time points (eg, when initiating conversion to XYWAV) but minimized during periods where participants are expected to be on a stable dose and regimen (eg, during the Baseline period, and the last two weeks of the 6-week, Intervention period).

The Baseline period involving an extended 2-week duration in which participants will remain on their currently prescribed, baseline Xyrem therapy has been included to provide more robust assessment of participant baseline data than provided in Study 15-006. The open-label design is deemed appropriate for this purpose, as efficacy of Xyrem and XYWAV has been previously established.

Specific study endpoints for assessments of safety, tolerability, effectiveness, participant preference, and ease of conversion from Xyrem to XYWAV are described in Section 3 and Section 8.2-3. The key descriptive endpoints for effectiveness, safety, and tolerability include changes in weekly rate of cataplexy attacks (for Narcolepsy Type 1 [NT1]), change in Epworth Sleepiness Scale (ESS) to assess EDS, Patient Global Impression of Change (PGIc), Adverse Events (AEs) and Serious AEs (SAEs), and change in nausea based on Nausea Visual Analog Scale [NVAS]. The treatment optimization endpoints include time to optimized dose and regimen, number of changes from the first dose and regimen to optimized dose and regimen, number of participants dosing fasted versus dosing without regard to food, and timing and characterization of meals relative to dosing. Additionally, exploratory endpoints will include ease of treatment conversion based on Ease of Switching Medication Scale (EOSMS) and medication preference based on Forced Preference Questionnaire (FPQ) assessments.

To decipher the clinical impact of dosing related to food, investigators will instruct participants to initiate XYWAV at the same dose and regimen as Xyrem with the first nightly dose taken at least 2 hours after meal. Once the investigator determines that a stable dose and regimen is established, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator. (Section 8.1.6).

Collectively, this study will expand the body of knowledge on the overall clinical experience in participants with narcolepsy transitioning from treatment with Xyrem to XYWAV.

4.3. Justification for Dose

Screening:

To be eligible for the study, participants must have been maintained on a stable, tolerable and effective dose and regimen of Xyrem (with or without any concomitant anticataplectics or stimulants) that will have remained unchanged for ≥ 2 months prior to study entry.

Baseline Period:

Participants will remain on a stable dose and regimen of Xyrem (and any concomitant anticataplectic or stimulant medications) during the 2-week Baseline period.

Treatment Conversion and Optimization Period:

Xyrem-stable participants will be initially switched to the same (gram-per-gram) dose and regimen of XYWAV (up to total nightly maximum dose of 9 grams, and with no single dose greater than 6 grams). Investigators will instruct participants initiating XYWAV to wait at least 2 hours prior to dosing, as with Xyrem (Xyrem USPI 2020). Once the investigator determines that a stable dose and regimen is achieved, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator (Section 8.1.6). Dose and regimen of any concomitant anticataplectics or stimulants will remain unchanged throughout the study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

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

5. STUDY POPULATION

The intended study population includes participants currently taking Xyrem for narcolepsy. Specifically, participants must have been maintained on a stable Xyrem dose and regimen, at any prescribed dose administered once, twice, or thrice nightly for no less than 2 months, up to a maximum nightly dose of 9 grams, with no single dose exceeding 6 grams.

Prospective approval of protocol deviations to recruitment and enrollment 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. Participant must be 18 to 80 years of age (inclusive), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have a primary diagnosis of Type 1 or Type 2 narcolepsy that meets ICSD-3 criteria or DSM-5 criteria (Ruoff and Rye 2016), and are being currently treated with Xyrem, with or without additional anticataplectics or stimulants.
3. Participants who have been taking Xyrem (with or without additional anticataplectics or stimulants eg, TCA, SNRI, SSRI, atomoxetine) in a stable dose and regimen for at least two months prior to screening, with evidence of clinical improvement on their current regimen, per the investigator's judgement. Only Xyrem will be substituted with XYWAV, with dose and regimen of any concomitant anticataplectics or stimulants remaining unchanged throughout the study.

Sex and Contraceptive/Barrier Requirements

4. 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 non-childbearing potential (WONCBP) as defined in Appendix 3

       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 3, 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) during screening (see Section 8.3.5).
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (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. Have a diagnosis of narcolepsy, secondary to another medical condition (eg, central nervous system injury or lesion)

2. Are currently prescribed a Xyrem regimen exceeding a dose of 9 grams nightly, or any single dose in excess of 6 grams.

3. Have been diagnosed with restless leg syndrome (RLS) requiring treatment other than iron supplements

4. Exhibit succinic semi-aldehyde dehydrogenase deficiency (SSADH)

5. Have uncontrolled hypothyroidism

6. Have a history of seizures, excluding early childhood non-pathological febrile seizures

7. Have a history of head trauma associated with loss of consciousness in the past 5 years, or if the event occurred more than 5 years prior to screening and the participant experiences sequelae due to the event

8. Show evidence of untreated or inadequately treated sleep-disordered breathing including:

    a. Presence of clinically significant and untreated obstructive or central sleep apnea (as determined by the investigator or documented previously); or one of the following:

    b. Apnea index (AI) >10 if on Obstructive Sleep Apnea (OSA) treatment or untreated, or

    c. Clinically significant hypoventilation, or

    d. Noncompliance with primary OSA therapy

Note: “Non-compliance” is defined as positive airway pressure use of $\leq$4 hours per night on $\leq$70% of nights ($\leq$5 of 7 nights/week) per historical report (with investigator concurrence) of use of an oral appliance on $\leq$70% of nights ($\geq$5 of 7 nights/week), or receipt of an effective surgical intervention for OSA symptoms.

9. Experience parasomnias (eg, sleep walking, REM Sleep Behavior Disorder, etc.) considered by the investigator to negatively impact the conduct of the study. Parasomnia events associated with physical injury to the participant (or others) shall be discussed with the sponsor Medical Monitor.

10. Meet criteria for current major depression based on clinical interview

11. Have any clinically relevant medical, behavioral, or psychiatric disorder (other than narcolepsy) that is associated with excessive sleepiness

12. Have a history or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria (Ruoff and Rye 2016)
13. Have a history or presence of any unstable or clinically significant medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or history or presence of another neurological disorder or surgical history that might affect the participant's safety and/or interfere with the conduct of the study, in the opinion of the investigator
14. Display relevant suicidality as indicated by Columbia Suicide Severity Rating Scale (C-SSRS) (Posner 2011) evaluation at screening
15. Display moderate to severe depression as indicated by the Participant Health Questionnaire – 9 (PHQ-9) (Kroenke 2001; Kroenke 2010) at screening
16. Are a female participant who is pregnant or breastfeeding

Prior/Concomitant Therapy

17. Have undergone treatment with any prohibited central nervous system (CNS) agents, including but not limited to benzodiazepines, non-benzodiazepine anxiolytics/ hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, or MCT inhibitors, eg, diclofenac, valproate, ibuprofen, within 2 weeks prior to enrollment. Discontinuation for the purpose of study enrollment is permitted only if considered safe by the investigator and approved by the Medical Monitors.

Prior/Concurrent Clinical Study Experience

18. Received any other investigational drug within 30 days or five half-lives (whichever is longer) prior to screening, or plan to use an investigational drug (other than the study intervention) during the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

1. Participants transitioning from Xyrem to XYWAV will be instructed to allow at least 2 hours after eating before dosing, until a stable dosing and regimen for XYWAV has been established.
2. Once a stable dosing and regimen is achieved, XYWAV may be taken with or without food and if needed, titrated to an optimized dose and regimen based on efficacy and tolerability under advisement and instruction from the investigator.

5.3.2. Caffeine, Alcohol, and Tobacco

1. There are no restrictions on participant use of caffeine and tobacco products in this study.
2. Participants will abstain from alcohol during the Screening period and during the study. Accordingly, results of the alcohol screening must be determined to be negative at Screening, before dosing for all participants and during the study, as measured during study visits indicated per the SoA (Section 1.3).

5.3.3. Other Restrictions

No additional restrictions are specified for this study.

5.3.4. Activity

Participants will be instructed to take the study drug while in bed and lie down immediately after dosing, as the study drug may cause them to fall asleep abruptly without feeling drowsy. No additional restrictions on activity are recommended for this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet the eligibility criteria. 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 serious adverse event (SAE).

Individuals who do not meet all eligibility criteria for participation in this study (screen failures) may be rescreened once, if the rescreening is approved by the Medical Monitor. Rescreening may occur following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (eg, unstable hypothyroidism) and is permitted only with the permission of the Medical Monitor. Participants who are approved for rescreening must be re-consented if re-screening occurs more than 28 days after the first consent, in which case, a new subject identification number should be assigned and all screening procedures should be repeated.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention Administration

Not applicable

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

For this study, the intervention/treatment is defined as intervention with XYWAV, administered to a study participant according to the study protocol.

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

The study interventions planned for use in this study are described below.

Table 4 Study Treatment/Intervention

Treatment Arm	Intervention/ Treatment Name	Formula-tion	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Use	Sourcing	Package	Labeling	Storage Conditions
1	JZP-258 (XYWAV)	Solution	0.5 g/mL (0.413 g/mL oxybate)	Maximum nightly dosage of 9 grams, administered once, twice or thrice nightly, with no single dose > 6 g **Intervention (Open-label Conversion and Treatment Optimization Period):** XYWAV will be initiated at equivalent (gram-per-gram) dose as prior Xyrem* regimen. Once a stable dose and regimen is achieved, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction from the investigator.	Oral	Experimental	Provided centrally by the sponsor	Study intervention medication will be provided in bottles with inserted Press-in Bottle Adapter [PIBA] (and accessories eg, dosing cups and dosing syringe), labeled per country-specific guidelines. All packaging and labeling operations per current Good Manufacturing Practices (cGMP) and local requirements and regulation. Child resistant packaging as required.	Open-label	Store at 25°C. Allowable excursions permitted to 15-30°C

Abbreviations: cGMP = current Good Manufacturing Practices; PIBA = press-in bottle adapter.
*Note: During the Baseline Period, participants will continue to take Xyrem (and any concomitant anticataplectics or stimulants) at the same dose and regimen as prescribed by their healthcare physician prior to enrollment in this study and using their own supply of Xyrem (and any other prescribed drugs), which will not be separately provided as part of this study.

6.2. Preparation/Handling/Storage/Accountability

Study intervention medication, XYWAV will be shipped to investigational sites, stored, inventoried, dispensed, returned to site, inventoried, and returned to sponsor or destroyed according to applicable country and local regulations for a controlled substance with instruction from Jazz.

1. Detailed guidance and information for the final disposition of study intervention is provided in the Pharmacy Manual located in the Investigator Trial Site Binder. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.
2. The investigator must have DEA license for Schedule III drugs and ensure compliance of storage with DEA-required security for CIII products. 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.
3. The investigator or designee will maintain accurate records of receipt of the study intervention including dates of receipt. Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
4. The investigator, institution, or the 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. Measures to Minimize Bias: Randomization and Blinding

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 once assigned, cannot be reassigned to another study participant. Study JZP258-401 is an open-label, single-arm trial, and therefore will have no blinding. Treatment allocation for this study will occur centrally through the use of an interactive response technology (IRT).

6.4. Study Intervention/Treatment Compliance

Jazz (sponsor) will provide the clinical site with open-label bottles of XYWAV oral solution 0.5 g/mL for all phases of the study.

The participant will self-administer study intervention(s) as directed by the study investigator and complete an electronic Food and Drug Dosing Diary (Appendix 4) daily. Completeness of the Food and Dosing Diary will be discussed and assessed at each visit beginning with Visit 2. Sites will counsel participants who have not been compliant with dosing and diary completion.

Measured compliance of treatment with the intervention will be maintained by counting the number of bottles of clinical study medication dispensed, which will be recorded on the investigational medicine record by the designated staff member. The volume of solution dispensed and returned will be recorded on the investigational medicine record. Sites will document observed discrepancy or missing bottles and assess abuse potential, when a difference of ≥ 30 mL per bottle between the returned volume and the expected returned volume.

A record of the quantity of study interventions dispensed to and administered by each participant will 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 at greater than the maximum allowable daily dose of 9 grams or any single dose exceeding 6 grams) will be recorded in the electronic case report form (eCRF). Sites are responsible for identification and documentation of missing bottles during the study.

6.4.1. Product Complaint Management

Complaints related to investigational products used in clinical studies are collected to ensure the safety of participants, to monitor product quality, and to ensure process and product improvements. Participants should be instructed to notify the investigator or study staff as soon as possible, if a complaint or problem is detected with XYWAV. The sponsor must be notified of the complaint, to facilitate assessment and appropriate response.

6.5. Dose Modification

Participants will be initially converted to XYWAV at the same dose as Xyrem (on a gram-per-gram basis), as described in Section 4.3 . Once the investigator determines that a stable dose and regimen is achieved, XYWAV may be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability (up to a maximum daily dose of 9 grams, with no single dose exceeding 6 grams), under advisement and instruction from the investigator.

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

No intervention following the end of the study or extension of study is currently planned.

Upon completing the ET or E/D assessments, including during the Safety Follow-up period, it is understood and expected that investigators will determine the appropriate course of care with the participant, with the option to resume medications that were discontinued prior to or during study participation.

6.7. Treatment of Overdose, Medication Errors, or Misuse

For this study, administration of XYWAV or Xyrem within a 24-hour time period, at a total dosage greater than 9 grams or a single dose greater than 6 grams will be considered an overdose.

In the event of an overdose of XYWAV or Xyrem, the investigator should:

- 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.
- Document the quantity of the excess dose as well as the duration of the overdose.

Medication errors are variances in the returned volume compared to the expected returned volume that are unintentional errors in dispensing or explainable (eg spilled bottle) or minor (< 30 mL difference) variances in administration of the study intervention.

Suspected misuse of the study intervention (XYWAV) should be investigated and participant counseled when a difference of ≥ 30 mL per bottle between the returned volume compared to the expected returned volume. Unreturned bottles must be requested through the end of study and documented reason if not returned to site. If not returned at final visit, site must document 3 attempts (where possible, 2 telephone calls and a certified letter to the participant) for return bottles after participant's completion of the study.

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 7.

6.8. Concomitant Therapy

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

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant treatment with certain prohibitory medications / therapies is not permitted during the study (Section 5.2, Exclusion Criteria; Prior/Concomitant Therapy). However, participants will continue to take any anticataplectics or stimulants at the same dose and regimen as prescribed by their healthcare physician, prior to enrollment in this study. Xyrem or any other medications prescribed to the participants prior to the study will not be provided as part of this 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 that 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 should be asked to return 2 weeks later for the Safety Follow-up Visit.

7.1. Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will not remain in the study, other than for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and safety follow-up, and for 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's alcohol screen result is positive
- The participant's urine drug screen test result is positive for any prohibited drugs in this study (see Section 5.2, Exclusion Criterion, 17)
- The participant has a positive serum pregnancy test (Appendix 3 and Section 8.3.5)
- The participant is non-compliant with study intervention or procedures
- The sponsor terminates the study prior to completion
- The investigator determines the participant should not continue on study intervention
- The participant enrolls in a different clinical study that involves investigational treatment considered by the sponsor to be incompatible with Study JZP258-401

7.1.1. Temporary Discontinuation/Study Intervention Interruption

In the unlikely event it is necessary for a participant to temporarily interrupt dosing (eg, between visits), whether the participant continues in the study will be determined by the site and appropriate sponsor personnel.

NOTE: If site restrictions or other limitations have the potential to impact safety of trial participants or the ability to conduct the study, mitigation strategies in alignment with the *FDA Guidance for Industry, Investigators, and Institutional Review Boards (IRB) entitled: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, updated 21-September- 2020)* may be necessary. Temporary interruptions or restrictions in performing study assessments and interventions related to COVID-19 will be documented by the investigational site and reported as 'unavoidable protocol deviations' in the Clinical Study Report.

Guidance on COVID-19 related considerations and mitigation strategies for oversight, data handling, and reporting will be outlined within specific Sponsor/Contract Research Organization (CRO) study plans.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an E/D visit should be conducted, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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 such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples (eg, for safety assessments) that are 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 he or she repeatedly fails (>2 times) to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow-up.
- The participant is not considered lost to follow up until the last scheduled visit for that individual participant.

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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor's Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA is essential and required for study conduct. Changes in study visit schedules or missed visits that lead to missing study information, must capture the specific information that explains the basis of missing data.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Screen failure reasons will be captured in the interactive response technology (IRT) system.
- After screening procedures have been completed and eligibility criteria have been confirmed, eligible participants will be provided with instructions on how to discontinue any excluded medications. Document that the investigator has determined that discontinuation is safe and medically appropriate, the Medical Monitor has approved, and the discontinuation is medically supervised.
- Diaries and Questionnaires will be in electronic format within a secure application uploaded to the subject's mobile phone or tablet computer device of choice for personal completion. Site personnel will be able to provide instruction for uploading, use, and completion of the electronic diaries (e-diaries) and electronic questionnaires (e-questionnaire). The application is secure with unique username and password for access.
- Lab analyte measures and ECGs will be read by qualified personnel at the site (eg, a physician)
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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.

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

Medical history of study participants 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, will 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, including over-the-counter medications, health, and dietary supplements. Any medication that is required to be washed out prior to the study should also be recorded. All medications currently taken by the participant should be recorded and reconciled for compliance with the protocol.

8.1.5. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the investigator to ensure the participant qualifies for the study.

8.1.6. Timing of Study Intervention Dosing

Participants will be instructed to dose XYWAV according to the following guidelines-

- On the first night of administering the study intervention drug (XYWAV), initiate treatment at the same dose and regimen as Xyrem, while maintaining the dose and regimen of any concomitant anticataplectics or stimulants unchanged throughout the study.
- Initially, as with Xyrem, wait at least 2 hours after the last meal before taking XYWAV.
- Once the investigator determines that a stable dose and regimen has been achieved, XYWAV can be taken with or without food. If needed, XYWAV will be titrated to an optimized dose and regimen based on efficacy and tolerability, under the advisement and instruction of the investigator.

8.2. Effectiveness Assessments

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

8.2.1. Rate of Cataplexy Incidents

The change in weekly rate of cataplexy attacks (for NT1) will be assessed. Participants will complete an electronic Cataplexy Frequency Diary (Appendix 5) each night prior to bedtime, to record the number of daily cataplexy attacks experienced, in accordance with the SoA (from the Baseline period through to the ET or E/D, as applicable). The study staff will review the diary at each study visit and discuss it with the subject at the phone/visit contact, see Section 9.4.2.

8.2.2. Epworth Sleepiness Scale

The ESS questionnaire (Johns 1991, Johns 2000, Broderick 2013) includes a set of 8 questions regarding how likely the participant would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze, to 3 = high chance of dozing. As such, the ESS provides a measure of EDS or average sleep propensity in daily life.

A self-administered, electronic ESS questionnaire will be completed by the participants at the baseline visit and the ET or E/D visits, as indicated in the SoA (Section 1.3), with appropriate training, instructions and supervision provided for completing the questionnaires, as needed.

8.2.3. Participant Global Impression of Change (PGIc)

The PGIc is a 7-point Likert-type rating based on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) that is widely used to assess efficacy in clinical drug trials (Schmitt 2014; Bogan 2017). The PGIc assessment will be administered in electronic format to participants at the ET or E/D visits, as indicated in the SoA (Section 1.3), with appropriate training, instructions and supervision provided for completing the assessment, as needed.

8.2.4. Dose and Regimen Changes in Intervention Period

To evaluate treatment optimization with XYWAV during the Intervention period, the number of changes from the first dose and regimen to an optimized dose and regimen and the time taken to achieve the optimized dose and regimen will be measured, as described in Section 9.4.2.

Additionally, the number of participants dosing fasted versus dosing without consideration of food, and the timing and characterization of meals with regard to dosing will be summarized descriptively. These assessments will utilize participant data collected using a self-administered, electronic Food and Drug Dosing Diary (Appendix 4) completed by participants daily (Section 9.4.2).

8.2.5. Ease of Switching Medication Scale (EOSMS)

To assess the ease of switching treatment from Xyrem to XYWAV, the EOSMS Questionnaire (Appendix 8) will be administered in electronic format to participants at the ET or E/D visits, as indicated in the SoA (Section 1.3).

8.2.6. Forced Preference Questionnaire (FPQ)

To evaluate participant preference for study medication, the FPQ Questionnaire (Appendix 9) will be administered in electronic format to participants at the ET or E/D visits, as indicated in the SoA (Section 1.3).

8.3. Safety and Tolerability Assessments

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

8.3.1. Physical Examinations

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

8.3.2. Vital Signs

- Vital signs to be measured (before blood collection, when applicable) will include oral temperature, heart rate (HR), respiratory rate (RR), and BP at the times specified in the SoA (Section 1.3).
- Blood pressure and pulse measurements will be assessed with a completely automated device.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes of rest period

8.3.3. Electrocardiograms

Single 12-lead ECG will be obtained for screening purposes only, as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, and QT intervals.

8.3.4. Clinical Safety Laboratory Assessments

Clinical laboratory assessments to be conducted in the study are listed in Table 5.

Table 5. List of Clinical Laboratory Tests

Hematology: - Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential **Urinalysis:** - Appearance - Bilirubin - Color - Glucose - Ketones - Nitrite - Occult blood - pH - Protein - Specific gravity - Urobilinogen - ***Serum Pregnancy Screen** **Drug Screen (urine)** **Alcohol Screen**	**Serum Chemistry:** - Albumin (ALB) - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT) - Aspartate aminotransferase (AST; SGOT) - Blood urea nitrogen (BUN) - Calcium (Ca) - Chloride (Cl) - Creatinine - Creatine kinase - Gamma-glutamyl transferase (GGT) - Globulin - Glucose - Lactate dehydrogenase (LDH) - Phosphorus - Potassium (K) - Sodium (Na) - Magnesium - Total bilirubin - Direct bilirubin - Total cholesterol - Total protein - Triglycerides - Uric acid - Thyroid stimulating hormone (TSH)(screening only)

*Pregnancy screening is required for all females of childbearing potential. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as >1 year of amenorrhea), who have medically documented ovarian failure (defined as serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.

- Clinical laboratory tests will be performed at the study time points indicated in the SoA (Section 1.3). Accordingly, certain clinical laboratory assessments (eg, comprehensive metabolic panel, hematology, urinalysis, TSH and serum pregnancy testing) will be performed for screening purposes only, whereas other clinical laboratory assessments (eg, urine drug and alcohol screening) will be performed at various study time points, as indicated per the SoA (see Section 1.3).
- All protocol-required laboratory tests (Table 5 and SoA) must be conducted in accordance with the laboratory manual.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing entry criteria.
- Pregnancy testing (serum) should be conducted as specified in the SoA (Section 1.3).
- Additional serum 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 participant's participation in the study.

8.3.6. Nausea Visual Analog Scale

Nausea is the most common adverse reaction observed in response to treatment with Xyrem leading to study discontinuation (incidence ≥ 5%). Tolerability associated with Xyrem and XYWAV will be measured based on an NVAS assessment (Appendix 6) administered electronically. The NVAS assessment will be completed by participants daily for the last 7 days of the Baseline (Xyrem-stable dose and regimen) period and the last 7 days on XYWAV of the Intervention period prior to ET, or prior to E/D if possible, as indicated in the SoA (Section 1.3).

8.3.7. Suicidal Ideation and Behavior Risk Monitoring

XYWAV and Xyrem are considered CNS depressants.

When informed consent has been given, families and caregivers of participants being treated with XYWAV (or Xyrem) should be alerted about 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 the Screening Visit, the Baseline/Screening version of the C-SSRS will be administered to participants to exclude any individuals with active suicidal ideation or behavior.

During the course of the study, participants who experience signs of suicidal ideation or behavior should undergo risk assessment. All factors contributing to suicidal ideation or behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

8.3.8. Participant Health Questionnaire–9 (PHQ-9)

The PHQ-9 represents a depression assessment scale that scores each of the nine DSM-IV diagnostic criteria for major depressive disorder in accordance with guidelines presented in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV). The PHQ assessment can be administered by self, study staff in person, or by telephone and is used to facilitate diagnosis of major depression and assessment of symptom severity. It is validated and documented in a variety of populations and is available in a variety of languages (Kroenke 2001).

In this study, PHQ-9 will be self-administered during the screening visit, as indicated in the SoA (Section 1.3). Participants will be evaluated and an assessment of risk will be made by a qualified mental health professional, if major depression is suspected or active suicidal ideation is identified.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AE and SAEs are presented in Appendix 7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 (Section 7).

Investigators are responsible for monitoring the safety of participants who enter the study and alerting the sponsor or it's designee of any event (unanticipated risk or benefit) considered unusual. Investigators are responsible for the appropriate medical care of participants in the study.

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 7.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs (including SAEs) will be collected from the time of signing of informed consent until the end of Safety Follow-up visit, at the various time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event by study personnel, as indicated in Appendix 7. 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 the 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 he/she considers 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 Adverse Events and Serious Adverse Events

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

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, 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 7.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards 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 relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (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 and then file it along with the investigator will also consult the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The Reference Safety Information (RSI) for the determination of expectedness of XYWAV can be found in the IB.

8.4.5. Pregnancy

- Serum pregnancy test will be performed at screening only.
- Details of all pregnancies in female participants and female partners of male participants after obtaining the necessary signed informed consent, will be collected after the start of study intervention and 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 female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While 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.
- Any post-study 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. While the investigator is not obligated to actively seek this information in former study participants / pregnant female partner, 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.

8.4.6. Overdose, Medication Errors, and Misuse

Overdose, medication errors, and misuse of the study intervention (defined in Section 6.7) must be recorded locally.

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 7.

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.

Information on signs and symptoms of XYWAV overdose is derived from reports of illicit misuse of GHB and are detailed in the IB. As with the management of all cases of drug overdosing, the possibility of multiple drug ingestion should be considered.

The healthcare provider is encouraged to consult with a regional poison control center for current treatment recommendations (IB).

8.5. Pharmacokinetics

Pharmacokinetic (PK) assessments will not be conducted in this study.

8.6. Genetics and/or Pharmacogenomics

Genetics will not be evaluated in this study.

8.7. Biomarkers

Biomarkers will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments will not be conducted in this study.

8.9. Health Economics

Health economics will not be assessed in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

All endpoints (listed in Section 3) will be summarized descriptively. Formal hypothesis testing will not be performed.

9.2. Sample Size Determination

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

9.3. Analysis Sets

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

Table 6. Study Analysis Sets

Participant Analysis Set	Description
Enrolled	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 CTMS), and inclusion/ exclusion from the Safety Analysis Set, including reasons for exclusion from it.
Safety	The Safety Analysis Set will include all participants in the Enrolled Analysis set who take at least one dose of Xyrem after providing informed consent. This analysis set will be used for summaries of all endpoints.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

9.4.1.1. Multiplicity Adjustments

As this study does not test a formal hypothesis, there is no multiplicity adjustment.

9.4.1.2. Definition of Study Periods for Analysis

The Baseline (Xyrem) Period refers to a 2-week duration in which participants remain on a stable Xyrem dose and regimen, with or without concomitant anticataplectics or stimulants. All data collected prior to the participant's first dose of XYWAV will be included in this period.

The Intervention (Open-label Treatment Conversion and Optimization) period refers to the 6-week duration in which the participant's treatment is transitioned from Xyrem to XYWAV. All data collected after the first dose of XYWAV will be included in this period (which does not include the Safety Follow-up period).

9.4.1.3. Statistical Methods

In general, categorical variables will be reported as frequency and percent. Continuous variables will be reported as the number of participants, mean, standard deviation (SD), or standard error (SE), median, minimum and maximum. All summaries, statistical analyses, and individual participant data

listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.4.1.4. Pooling of Investigational Centers

Data from all investigational centers will be pooled for presentation of the main results (demographics, safety, tolerability, effectiveness, participant preference, and ease of conversion). Data may be pooled as appropriate, for exploratory analyses.

9.4.1.5. Dropouts and Missing Data

Participants who drop out of the study will not be replaced. All reported data will be included in summaries without imputation of any missing data, with the exception of diary data for cataplexy attacks as noted in Section 9.4.2 and NVAS, as noted in Section 9.4.4.

9.4.2. Effectiveness Endpoints

Effectiveness endpoints will be summarized descriptively. The following effectiveness endpoints will be assessed in this study:

- Change in weekly rate of cataplexy attacks: Participants will be required to complete an electronic Cataplexy Frequency Diary (Appendix 5) daily. Based on these data, the weekly rate of cataplexy attacks (for NT1) will be established. Additionally the change in weekly cataplexy rate from the last week of the Baseline period (on Xyrem) to that of individual weeks during the Open Label Conversion and Treatment Optimization Period will be summarized. For participants experiencing at least 1 day of cataplexy attack, the weekly number of cataplexy attacks will be derived as the average number of daily attacks from days with non-missing data within the week, multiplied by 7.
- Change in Epworth Sleepiness Scale (to assess EDS): Changes in ESS scores between the Baseline period and ET or E/D, as applicable, will be summarized.
- Participant Global Impression of Change: PGIc values will be measured at the ET or E/D, as applicable, in accordance with the SoA (Section 1.3). The number of participants with each response will be summarized. Additional categorization of the scores may be performed and summarized.
- Time to optimized dose and regimen is defined as the time from the first dose and regimen to the optimized dose and regimen of XYWAV, where the optimized dose and regimen indicates the final dose and regimen that remains unchanged throughout the remainder of the Intervention (Open-label Conversion and Treatment Optimization) period. Compliance is not considered in the derivation of the time to achieve optimized dose and regimen. The time to achieve optimized dose and regimen will be summarized.
- Additionally, the number of changes from the first dose and regimen to optimized dose and regimen, the number of participants dosing fasted versus dosing without consideration of food, and the timing and characterization of meals with regard to dosing of XYWAV (Appendix 4) will be summarized descriptively.

9.4.3. Exploratory Endpoint(s)

The following exploratory endpoints will be assessed and summarized in this study-

- Ease of Switching Medications Scale (EOSMS)

  The EOSMS Questionnaire (Appendix 8) was developed for this study to rate the ease of the process of switching to XYWAV, ranging from extremely easy to extremely difficult and will be administered at the ET or E/D visits (Section 1.3).

- Forced Preference Questionnaire (FPQ)

  The FPQ (Appendix 9) was developed for this study and will be administered during the ET or E/D visits, as indicated in the SoA (Section 1.3).

9.4.4. Safety And Tolerability Analysis

All safety and tolerability analyses will be conducted in the Safety Population, based on key endpoints are summarized below. Additionally collected safety data will be summarized, as appropriate.

Adverse Event Analyses

AEs will be mapped to system organ classes (SOC) and preferred terms (PT) in alignment with Medical Dictionary for Regulatory Activities (MedDRA) criteria. AEs are defined in this study as follows (Appendix 7).

- A 'Xyrem-emergent AE' refers to an AE that began or worsened in the period following signing of the informed consent and before administration of the first study intervention (XYWAV) dose (ie, including the Screening period through the Baseline [Xyrem-stable dose and regimen] period)
- A treatment-emergent adverse event (TEAE) refers to an AE that either began or worsened after administration of the first dose of study intervention drug (XYWAV) to ET (prior to the Safety Follow-up period).
- Unless specified, the term AE will include both Xyrem-emergent AEs and TEAEs
- Any AEs occurring in the post-intervention Safety Follow-up period will not be considered as either Xyrem-emergent AEs or TEAE; these will not be included as part of safety and tolerability analyses, but listed separately.

Xyrem-emergent AEs (overall and during the Baseline period), TEAEs, SAEs, AEs leading to discontinuations and fatal AEs will be summarized. All AEs will be summarized by maximum severity.

The population incidence of Xyrem-emergent AEs, TEAEs, SAEs, AEs leading to discontinuations and any fatal AEs will be presented by MedRA SOC and PT categories. PT summaries may also be provided, as appropriate.

If a participant has multiple events with the same PT occurring in different periods, the event will be reported for each of those periods. Multiple increases in severity will only be counted as one AE.

Nausea Visual Analog Scale (NVAS)

The NVAS (Appendix 6) evaluation was developed for this study, and will be performed daily over the last 7 days of the Xyrem-stable Baseline period and the last 7 days on XYWAV of the Intervention period prior to ET visit or prior to the E/D, if possible. For participants with at least one day of NVAS data, the NVAS for that week will be the average daily score from days with non-missing data within the week, then multiplied by 7. The mean of each assessed 7-day period will be summarized and the change from the mean of the Baseline period to the mean of the Intervention period will be summarized.

9.4.5. Pharmacokinetic Assessments

No PK assessments will be performed in this study

9.5. Interim Data Analysis

Based on enrollment, an optional interim analysis may be conducted after approximately the first 25 participants and 50 participants respectively, have completed or prematurely terminated the study to

provide an early understanding of the clinical experience of participants switching from Xyrem to XYWAV. This data may be presented externally. This process will occur with no pause in enrollment.

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

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

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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 before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require IRB/IEC approval prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Notifying the sponsor of SAEs or other significant safety findings, as specified in Section 8.4.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (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.
  - Acknowledgment of his/her agreement with the protocol, by signing the protocol signature page herein and providing to the sponsor

10.1.2. Financial Disclosure

Investigators and sub-investigators 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. The sponsor (or designee) may contact study staff and/or the investigator approximately 1 year after study completion to confirm accurate financial information.

10.1.3. Informed Consent Process

- The investigator or his/her 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and 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).
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.1.4. Data Protection

- 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 or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator must ensure access to the source documents (or certified copies) and study records, as required by sponsor and/or regulatory authorities.

10.1.5. Committees Structure

- Establishing a Data Monitoring Committee is not planned for this trial.
- Establishing an internal safety review committee is not planned for this trial.
- Participant safety will be continuously monitored by the sponsor via routine internal safety review, which includes safety signal detection, review of any treatment related SAEs and death regardless of causality at any time during the study.
- In addition, periodic review of the accumulating safety data will be performed. Reports of safety findings (from either single events or based on aggregate review) that suggest a

significant risk to humans will be distributed to all participating investigators and to the relevant regulatory authorities and IRBs/IECs.

10.1.6. Dissemination of Clinical Study Data

As the sponsor of the study, Jazz 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. The results of primary outcome measures will be reported with required study information on clinical trial registries, as applicable. Results of exploratory outcomes measures may or may not be reported.

10.1.7. Data Quality Assurance

- Investigators and site staff will be trained on protocol procedures and eCRF completion prior to enrolling participants in the study.
- All participant data relating to the study will be recorded on printed 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 case report form (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, CROs).
- 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 for the existence 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. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification 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 study start date is the date on which the first participant has the first visit.

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. At study completion, the investigator must notify the IRB/IEC, and the Sponsor will notify regulatory authorities.

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:

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
- Target number of participants is attained earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO 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 assure appropriate participant therapy and/or follow-up care.

In the event that an IRB/IEC terminates a study, or suspends study approval at a research site, the investigator must notify the Sponsor, inform study participants, and ensure appropriate participant therapy and/or follow-up care.

10.1.10. Publication Policy

The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice. The participation of the investigator and other trial personnel as a named author shall be determined in accordance with sponsor policy and generally accepted standards for authorship such as the International Committee of Medical Journal Editors (ICMJE) recommendations, and maybe updated from time to time. Publication agreements will be addressed within Investigator/Site Clinical Trial Agreements.

APPENDIX 1. ABBREVIATIONS AND DEFINITIONS

Abbreviations	Descriptions
AASM	American Academy of Sleep Medicine
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
AI	Apnea index
BP	blood pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
E/D	Early Discontinuation
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime sleepiness
EOSMS	Ease of Switching Medications Scale
ESS	Epworth Sleepiness Scale
ET	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FPI	first participant in
FPQ	Forced Preference Questionnaire
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GHB	gamma hydroxybutyrate
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSD	International Classification of Sleep Disorders
IEC	Independent Ethics Committee
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	interactive response technology
IUD	Intrauterine device

IUS	Intrauterine hormone-releasing system
Jazz	Jazz Pharmaceuticals
LPO	last participant out
MedDRA	Medical Dictionary for Regulatory Activities
NT1	Narcolepsy Type 1
NVAS	Nausea Visual Analog Scale
OLE	open-label extension
OREs	Other Reportable Experiences
OSA	Obstructive Sleep Apnea
PE	physical examination
PGIc	Participant Global Impression of Change
PHQ-9	Participant Health Questionnaire-9
PK	Pharmacokinetic
PT	preferred term
RDA	recommended dietary allowance
REM	rapid eye movement
RLS	restless leg syndrome
RSI	Reference Safety Information
SAE	serious adverse event
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SNRI	serotonin norepinephrine reuptake inhibitor
SoA	Schedule of Activities
SOC	System Organ Class
SSADH	succinic semi-aldehyde dehydrogenase deficiency
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse event
UA	Urine Analysis
US	United States
USA	United States of America
USPI	US Prescribing Information
V	Visit
W	Week
WOCBP	women of childbearing potential
WONCBP	woman of non-childbearing potential

APPENDIX 2. REFERENCES

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APPENDIX 3. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Childbearing Potential (WOCBP)

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

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their 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:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to 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.

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 the 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 (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX 4. FOOD AND DRUG DOSING DIARY

A. Drug taken: Xyrem

Subject Number: _____

Date: _____

1. What was the time of the first dose?

(HH:MM)

_____

2. What was the end time of the last meal prior to the first study drug dose?

(HH:MM)

_____

3. Indicate type of meal below-
   - ☐ Regular Meal- food consumed as part of dinner or planned occasion
   - ☐ Snack- a bite to eat consumed between meals or prior to bed
   - ☐ Beverage- a liquid drink (eg, tea, juice, milk), other than water

---

B. Drug taken: XYWAV

Subject Number: _____

Date: _____

1. What was the time of the first dose?

(HH:MM)

_____

2. What was the end time of the last meal prior to the first study drug dose?

(HH:MM)

_____

3. Indicate type of meal below-
   - ☐ Regular Meal- food consumed as part of dinner or planned occasion
   - ☐ Snack- a bite to eat consumed between meals or prior to bed
   - ☐ Beverage- a liquid drink (eg, tea, juice, milk), other than water

APPENDIX 5. CATAPLEXY FREQUENCY DIARY

Definition of cataplexy attack:

A cataplexy attack can:

1. Cause you to actually fall down or you would have fallen if you did not support yourself or:
2. Make part of your body feel weak.

Participants will be asked to complete the Cataplexy Frequency Diary each night prior to bedtime.

Minimally the following information will be collected on the diary:

Date

_____

Total daily number of cataplexy attacks (0 will be recorded if no attacks occurred).

_____

APPENDIX 6. NAUSEA VISUAL ANALOG SCALE (NVAS)

Please select the point on the line below that represents your level of long-lasting nausea that persists throughout the day.

Over the **past 24 hrs**, how severe was your nausea?

APPENDIX 7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
In this study, an AE is any untoward medical occurrence in a clinical study from the time of participant's informed consent, temporally associated with the use of study intervention (XYWAV) or Xyrem (during the Baseline period), whether or not considered related to the study intervention (XYWAV) or Xyrem, respectively. Specifically, • AEs associated with the study intervention (XYWAV) are referred to as treatment emergent AEs or TEAEs • AEs associated with the use of Xyrem (during the initial Baseline period) will be referred to as Xyrem-emergent AEs • Unless specified, the overall term AE will encompass both Xyrem-emergent and XYWAV-related TEAEs 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 (XYWAV) or Xyrem (in the Baseline period).

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, 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 and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose, medication error, or misuse of either study intervention or a concomitant medication. Overdose, medication error or misuse per se will not be reported as an AE/SAE unless it is an intentional overdose or illicit misuse taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 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 serious adverse event that, at any dose:

a. Results in death

b. 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, which hypothetically might have caused death, if it were more severe.

c. Requires in-patient 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.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. 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, it is the responsibility of the investigator to review 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 1 of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only • Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). • Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • Life-threatening: life-threatening consequences; urgent intervention indicated. • Fatal: death related to adverse event When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • 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. • The investigator will also consult the investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • 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 his/her 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.
- 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

SAE Reporting to the sponsor or designee via an Electronic Data Collection Tool

- SAEs must be reported to the sponsor (or designee) using an SAE Reporting Form within 24 hours of first knowledge of the event by study personnel.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The form, instructions on completion and contact information can be found in the investigator trial binder.
- The SAE Reporting Form should be completed as much as possible before transmittal.
- Contacts for SAE reporting can be found in the investigator trial binder.

Reporting of Other Reportable Experiences (OREs)

- OREs must be reported to the sponsor or its designee using an ORE Reporting Form within 24 hours of first knowledge of the event by study personnel.
- The form, instructions on completion and contact information can be found in the investigator trial binder.
- The ORE Reporting Form should be completed as much as possible before transmittal.
- Contacts for ORE reporting can be found in the investigator trial binder.

APPENDIX 8. EASE OF SWITCHING MEDICATIONS SCALE

Ease of Switching Medications:

The process of switching to the new medication was:

- ☐ Extremely Easy, Not Difficult At All
- ☐ Easy
- ☐ Neither Easy nor Difficult
- ☐ Difficult
- ☐ Extremely Difficult, Not Easy At all

APPENDIX 9. FORCED PREFERENCE QUESTIONNAIRE

Thinking about your experience with Xyrem and XYWAV, which would you prefer to treat your narcolepsy?

- ☐ Xyrem
- ☐ XYWAV

Please state the main reason for your preference below:

[Free Text]