

Xyrem® (sodium oxybate) oral solution  
Clinical Study Protocol: 13-005 Amendment 5

Jazz Pharmaceuticals

## Clinical Study Protocol: 13-005

**Study Title:** A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy

**Study Phase:** Phase 2/3

**Product Name:** Xyrem® (sodium oxybate) oral solution

**IND Number:** 49,641

**EUDRACT Number:** 2014-001389-93

**Indication:** Pediatric Cataplexy in Narcolepsy

**Investigators:** Multicenter

**Sponsor:** Jazz Pharmaceuticals  
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**Medical Monitor:** [REDACTED]

**Contract Research Organization:** [REDACTED]

**Clinical Laboratory:** [REDACTED]

<b>Original Protocol:</b>	14 April 2014
<b>Amendment 1:</b>	29 August 2014
<b>Amendment 2:</b>	1 April 2015
<b>Amendment 3:</b>	05 August 2015
<b>Amendment 4:</b>	05 April 2016
<b>Amendment 5:</b>	23 February 2017

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This study will be conducted under Good Clinical Practice guidelines.

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## SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
FINISHED PRODUCT	Xyrem® (sodium oxybate) oral solution
STUDY NUMBER	13-005
STUDY PHASE	Phase 2/3
TITLE	A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy
LOCATIONS	This study will be conducted globally at approximately 70 sites
OBJECTIVES	<p>Primary objectives are:</p> <ol style="list-style-type: none"> <li>1) To evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy</li> <li>2) To evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to one year (and potentially more than one year in some subjects participating in a continuation of the open-label safety evaluation)</li> </ol> <p>Secondary objectives are:</p> <ol style="list-style-type: none"> <li>1) To evaluate the efficacy of Xyrem in the treatment of excessive daytime sleepiness (EDS) in pediatric subjects with narcolepsy with cataplexy</li> <li>2) To characterize the pharmacokinetics (PK) of Xyrem in pediatric subjects (ages 7-17 years) with narcolepsy with cataplexy</li> <li>3) To evaluate the safety of titrating Xyrem in pediatric subjects to an effective and tolerable dose</li> </ol>
DESIGN	<p>Under Amendment 5, this study is divided into two parts: Part 1 includes one year of treatment, and Part 2, the Open-Label Continuation Period, provides the opportunity to continue treatment for up to an additional 2 years.</p> <p><b><u>Part 1</u></b> Part 1 of this study was initially designed as a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution. As a result of a preplanned interim analysis, which demonstrated positive efficacy results on the primary efficacy endpoint, the protocol was amended</p>

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	<p>(Amendment 4) to replace placebo treatment in the Double-Blind Treatment Period with open-label Xyrem treatment. After Amendment 4 becoming effective, all subjects entering the Double-Blind Treatment Period will receive open-label Xyrem treatment. For administrative reasons, the term “Double-Blind Treatment Period” will continue to be used throughout the protocol. Following the Double-Blind Treatment Period (2 weeks), this study also includes an open-label safety extension allowing subjects to continue Xyrem treatment for up to one year in Part 1.</p> <p>In addition, the PK of Xyrem will be evaluated in a subset of subjects. Children and adolescents, diagnosed with narcolepsy with cataplexy who are currently treated with Xyrem or are Xyrem naïve, with or without concomitant stable stimulant use, are eligible to enter the study. For this study, a Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Part 1 Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).</p> <p>All subjects will be evaluated for eligibility during the Part 1 Screening Period (up to 30 days [if needed, additional time may be granted with permission of the Medical Monitor]).</p> <p>Following Part 1 screening, subjects who are Xyrem naïve will enter the Open-Label Titration Period of up to 10 weeks. Once the Xyrem dose has been optimized per the Investigator’s judgment, these subjects may enter the open-label Stable-Dose Period with that dose. Subjects who are on Xyrem at study entry will remain on their stable dose and regimen (i.e., two equally divided doses or two unequally divided doses) of Xyrem and enter the Stable-Dose Period following screening.</p> <p>Subjects are eligible to enter the Double-Blind Treatment Period if the dose and regimen of Xyrem remains unchanged during the Stable-Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events due to Xyrem treatment have occurred.</p> <p>Subjects entering the Double-Blind Treatment Period prior to Amendment 4 becoming effective, had been randomized 1:1 to receive one of the following two treatments during the 2-week Double-Blind Treatment Period (randomized-withdrawal):</p> <ul style="list-style-type: none"><li>• <b>Xyrem:</b> Active Xyrem will be continued as a double-blind treatment at the stable dose taken and regimen used in the prior 2 weeks</li></ul>
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	<ul style="list-style-type: none"> <li>• <b>Xyrem placebo:</b> Xyrem placebo will be initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.</li> </ul> <p>Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment in this period.</p> <p>Subjects who complete the entire Double-Blind Treatment Period will be eligible to continue in the Open-Label Safety Period. The Open-Label Safety Period will allow subjects to continue Xyrem treatment for up to one year in Part 1.</p> <p>In addition, at certain study sites, a subset of subjects on a stable dose of Xyrem will participate in an open-label PK evaluation during Part 1. Subjects will be stratified to two age groups: 7-11 years of age and 12-17 years of age. Up to 18 subjects in each of the two age groups will be eligible to participate in the PK evaluation. Every effort will be made to ensure a minimum of 12 subjects in each age group complete the PK assessments. However, when sufficient data are obtained to characterize the PK profile with adequate precision during the study, as determined by the Data and Safety Monitoring Board (DSMB), or when enrollment of 100 subjects in the study has been reached, enrollment in the PK evaluation will stop and existing data will be analyzed and reported. These subjects will have a limited number of blood samples taken while on Xyrem at the clinic to measure sodium oxybate concentrations. Samples will be taken at the following times relative to the first Xyrem dose: 0 (pre-dose), 0.75, 1.5, 2.5, and 4 hours (pre-2nd dose) to characterize the PK of the first Xyrem dose, and at 4.75 and 8 hours to characterize the peak and residual exposure associated with the second Xyrem dose (total blood volume for PK samples is 40 mL taken over a minimum of 2 days). Subjects evaluated for PK will also undergo all other study procedures specified in the protocol.</p> <p><b><u>Part 2</u></b></p> <p>Upon approval of Amendment 5, subjects who complete one year in the study (Part 1) will have the opportunity to continue open-label Xyrem treatment in Part 2 until the first occurrence of any of the following:</p> <ul style="list-style-type: none"> <li>• Up to an additional 2 years</li> <li>• Until the subject reaches 18 years of age</li> <li>• Until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI)</li> </ul> <p>Subjects who have already completed Part 1 may re-enroll in Part 2.</p>
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ESTIMATED DURATION OF STUDY	It is anticipated that enrollment in Part 1 will be completed within 2 years. The estimated duration of the study (Parts 1 and 2) will be approximately 4 years.
STUDY POPULATION	<p>The study will enroll pediatric subjects who are diagnosed with narcolepsy with cataplexy, who have provided assent, and whose parent(s) or guardian(s) have signed the informed consent form in accordance with local IRB/IEC requirements. At least 100 subjects will be enrolled in the study. Every effort will be made to enroll approximately 30 subjects on Xyrem at study entry of the anticipated 100 subjects enrolled. Other subjects enrolled will be Xyrem naïve at study entry.</p> <p>A subset of the subjects who are taking Xyrem at a stable dose for their narcolepsy symptoms will participate in the PK evaluation during Part 1.</p> <p>Subjects who have completed one year in the study (Part 1) may be eligible for up to an additional 2 years of treatment in Part 2.</p>
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Children and adolescents who are diagnosed with narcolepsy with cataplexy and who are currently treated with Xyrem or are Xyrem naïve, with or without concomitant stable stimulant use, are eligible to enter the study.
TEST PRODUCT	<p>Xyrem (sodium oxybate) oral solution</p> <p>Xyrem placebo (sodium citrate) oral solution (Placebo treatment only applicable to subjects who had already entered the Double-Blind Treatment prior to Amendment 4 becoming effective)</p> <p>Flavorant that can be added to the water that is used as diluent will be provided, if available, for study drug preparation if flavored diluent is requested by the subject/parent/guardian for palatability.</p>
REFERENCE PRODUCT	None
DURATION OF TREATMENT	The treatment duration for each subject in Part 1 of the study will be approximately 52 weeks. Eligible subjects may participate in Part 2 for up to an additional 2 years or until they reach 18 years of age or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first. The total duration of a subject's treatment during the study will be up to 3 years.
EFFICACY ASSESSMENTS	For subjects who entered the Double-Blind Treatment Period prior to Amendment 4 becoming effective, all efficacy assessments will be comparisons of the measurement made during, or at the end of, the last 2 weeks of the Stable-Dose Period compared with the 2 weeks of Double-Blind Treatment Period. These assessments will continue to be collected during the Stable Dose and Double Blind Periods after

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	<p>Amendment 4 becoming effective.</p> <p>Primary endpoint:</p> <ol style="list-style-type: none"> <li>1. Change in weekly number of cataplexy attacks.</li> </ol> <p>Key secondary endpoints:</p> <ol style="list-style-type: none"> <li>2. Clinical Global Impression of Change (CGIc) for cataplexy severity</li> <li>3. Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD]) score</li> </ol> <p>Other secondary endpoints:</p> <ol style="list-style-type: none"> <li>4. CGIc for narcolepsy overall</li> <li>5. Change in Quality of Life (QoL) (SF-10)</li> </ol> <p>Exploratory endpoints:</p> <ol style="list-style-type: none"> <li>6. Change in weekly school attendance (if enrollment overlaps with school attendance period)</li> <li>7. Patient Global Impression of Change (PGIc) for narcolepsy overall</li> </ol>
<p><b>SAFETY ASSESSMENTS</b></p>	<p>Safety will be assessed at time points specified in the schedules of events, as well as throughout the study. Safety assessments will include the following:</p> <ul style="list-style-type: none"> <li>• Adverse event (AE) monitoring</li> <li>• Vital signs</li> <li>• Physical examinations (including weight and height)</li> <li>• 12-lead ECG</li> <li>• Polysomnography (PSG) parameters (including respiratory measures)</li> <li>• Clinical laboratory tests (chemistry, hematology, and urinalysis)</li> <li>• Assessments of growth and precocious puberty</li> <li>• C-SSRS for emergent suicidality</li> <li>• CDI 2:SR[S] for emergent or worsening depression</li> <li>• MASC-10 for emergent or worsening anxiety</li> <li>• Serum pregnancy tests (if applicable)</li> </ul> <p>Exploratory endpoint:</p> <ul style="list-style-type: none"> <li>• CO<sub>2</sub> monitoring (end tidal CO<sub>2</sub> [EtCO<sub>2</sub>] or transcutaneous CO<sub>2</sub> [TcCO<sub>2</sub>]) in sites where monitoring is routinely performed and performance will not negatively impact study participation or PSG data integrity</li> </ul> <p>A DSMB will review the safety data on a regular basis.</p>
<p><b>PHARMACOKINETIC VARIABLES</b></p>	<p>The PK parameters for plasma sodium oxybate concentrations include: the area under the plasma concentration time curve (AUC), maximum plasma drug concentration (C<sub>max</sub>), and time to maximum plasma drug concentration (T<sub>max</sub>), over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours (0.75 hours after the 2<sup>nd</sup> dose) and 8 hours (4 hours after 2<sup>nd</sup> dose) will be</p>

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	<p>measured to estimate peak and residual exposure associated with the 2<sup>nd</sup> nighttime dose. Dose proportionality will be based on the ratio of AUC values for each subject. Pharmacokinetics will be summarized for the 7-11 and 12-17 year age groups, and a comparison to historical PK data in adults will also be made.</p>
<p>STATISTICAL ANALYSIS</p>	<p><b>To address Primary Objective 1 and Secondary Objective 1:</b> A tiered approach was planned to control the Type 1 family-wise error rate at the 0.05 significance level with all tests being two-sided for testing of the primary and secondary efficacy endpoints.</p> <p>Due to the positive primary efficacy results from the pre-specified interim analyses, the DSMB recommended to stop the Double-Blind Randomized-Withdrawal Period. Tiered testing on secondary endpoints, as defined below, will be conducted with a significance level of 0.05, with all tests being two-sided.</p> <p><b>Tier 1: Primary endpoint</b> Change in weekly number of cataplexy attacks from the last 2 weeks of the Stable-Dose Period to the 2 weeks of the Double-Blind Treatment Period. The primary endpoint demonstrated efficacy at the interim analysis with a significance level &lt;0.005. Testing will continue with Tier 2.</p> <p><b>Tier 2: Key secondary endpoint #2</b> CGIc for cataplexy severity from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 3 tests will be conducted.</p> <p><b>Tier 3: Key secondary endpoint #3</b> Change in the ESS (CHAD) score from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 4 tests will be conducted.</p> <p><b>Tier 4: Other secondary endpoint #4</b> CGIc for narcolepsy overall from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 5 tests will be conducted.</p> <p><b>Tier 5: Other secondary endpoint #5</b> Change in QoL (SF-10) from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period</p>

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	<p>The testing of this endpoint will be conducted at the 0.05 significance level.</p> <p>Exploratory efficacy endpoints will be tested without multiplicity adjustments. For these parameters, nominal p-values will be reported. Non-categorical efficacy parameters will be analyzed by non-parametric analysis of covariance (ANCOVA). Ordinal categorical parameters, including CGIc and PGIc, will be analyzed using Cochran–Mantel–Haenszel (CMH) tests for row mean score difference.</p> <p>Efficacy data in the open-label phase will be summarized by visit.</p> <p><b>To address Primary Objective 2 and Secondary Objective 3:</b> Safety will be summarized using descriptive statistics and reported separately for Part 1 and Part 2 as well as across the entire study (Part 1 and Part 2) for select analyses. Adverse events will be assessed for subpopulations including Xyrem naïve, subjects on Xyrem at study entry, Ages 7-11, and Ages 12-17, as applicable. When summarizing data across the entire study by subpopulations, subjects are analyzed according to their initial enrollment status. For Part 1, adverse events will also be summarized by treatment group and by dose. Safety analyses will also include an analysis of the nadir oxygen saturation level at each dose, and number and duration of any confirmed desaturations below 90%, 80%, 70%, 60% and 50% on PSG nights excluding the screening PSG. For Part 2, safety data will be summarized by Ages 7-11, Ages 12-17, and overall.</p> <p><b>To address Secondary Objective 2:</b> Concentration data for sodium oxybate will be summarized by sampling time point and by PK parameter using descriptive statistics for each age group and overall. Dose proportionality will be assessed from the ratio of AUC and C<sub>max</sub> values. The ratios and their 90% confidence intervals will be presented. If warranted, regression models will be used to explore the relationship between plasma concentration and dose on a mg/kg basis.</p> <p>An ongoing analysis of the PK data will also be conducted to characterize the PK of Xyrem in children and adolescents.</p>
DATE OF ORIGINAL PROTOCOL	14 April 2014
AMENDMENT 1	29 August 2014
AMENDMENT 2	1 April 2015
AMENDMENT 3	05 August 2015
AMENDMENT 4	05 April 2016
AMENDMENT 5	23 February 2017

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADI	Acceptable daily intake
AE	Adverse event
AHI	Apnea hypopnea index
AI	Apnea index
ALB	Albumin
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AR	Adverse reaction
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration time curve
BMI	Body mass index
BUN	Blood urea nitrogen
C <sub>max</sub>	Maximum plasma drug concentration
Ca	Calcium
CBC	Complete blood count
CDI 2:SR[S]	Children's Depression Inventory 2 <sup>nd</sup> Edition Self-Report Short Version
CFR	Code of Federal Regulations
CGIc	Clinical Global Impression of change
CGIs	Clinical Global Impression of severity
cGMP	Current Good Manufacturing Practice
CHQ	Child Health Questionnaire
Cl	Chloride
CMH	Cochran–Mantel–Haenszel
CNS	Central nervous system
CO <sub>2</sub>	Carbon dioxide
CRF	Case report form

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CRO	Contract Research Organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DMP	Data management plan
DNS	Disrupted nighttime sleep
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
EMLA	Eutectic mixture of local anesthetics
ESS	Epworth Sleepiness Scale
ESS (CHAD)	ESS for Children and Adolescents
EtCO <sub>2</sub>	End tidal CO <sub>2</sub>
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GH	Growth hormone
GHB	Gamma-hydroxybutyrate
GVP	Good Pharmacovigilance Practice
hCG	Human chorionic gonadotropin
HLA	Human Leukocyte Antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
ICSD	International Classification of Sleep Disorders

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IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K	Potassium
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MASC-10	Multidimensional Anxiety Scale for Children 10 Item
MSLT	Multiple Sleep Latency Test
Na	Sodium
NDA	New Drug Application
OSA	Obstructive Sleep Apnea
OTC	Over the counter
PD	Pharmacodynamics
PGIc	Patient Global Impression of change
PI	Prescribing information
PK	Pharmacokinetics
PSG	Polysomnography
PT	Prothrombin time
PTT	Partial thromboplastin time
QoL	Quality of life
REM	Rapid eye movement
REMS	Risk Evaluation and Mitigation Strategy
RLS	Restless leg syndrome

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SAE	Serious adverse event
SF-10	SF-10 for Children
SmPC	Summary of Product Characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitor
SOP	Standard operating procedure
SpO <sub>2</sub>	Oxygen saturation
SSADH	Succinic semi-aldehyde dehydrogenase deficiency
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reactions
Suspected AR	An AE for which there is a lesser degree of certainty about causality than an adverse reaction
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SOREMPs	Sleep onset REM periods
TcCO <sub>2</sub>	Transcutaneous CO <sub>2</sub>
TCA	Tricyclic antidepressant
T <sub>max</sub>	Time to maximum plasma concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WMA	World Medical Association

## 1 INTRODUCTION

Xyrem (sodium oxybate) oral solution (NDA 21-196) is approved in the United States (US) for the treatment of cataplexy in patients with narcolepsy (2002) and for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy (2005). Xyrem is also approved in Canada for the treatment of cataplexy in patients with narcolepsy (2005) and in the European Union (EU) for the treatment of cataplexy in adult patients with narcolepsy (2005) and for use in the treatment of narcolepsy with cataplexy in adult patients with narcolepsy (2007). Xyrem is currently marketed in the US, Canada, and 20 European countries.

Xyrem has been on the US market for more than 14 years. It is a Schedule III controlled substance available only through a restricted distribution program managed by the Central Pharmacy under a Risk Evaluation and Mitigation Strategies (REMS). Xyrem is a CNS depressant and is taken at night in two equally divided doses.

Narcolepsy is a life-long neurologic disease for which no cure has been identified. It affects an estimated 0.02% to 0.067% of the population worldwide and approximately 1 in 2000 individuals in the United States (Ohayon 2007, Majid & Hirshkowitz 2010) and 4.7 of 10,000 (0.047%) individuals in the general population of five European countries (United Kingdom (UK), Germany, Italy, Portugal, and Spain) (Ohayon et al. 2002). The symptomatology of this condition is well described in the literature, with consensus on the five core symptoms of narcolepsy: EDS, cataplexy, sleep paralysis, sleep-related (hypnagogic and hypnopompic) hallucinations, and disrupted nighttime sleep (DNS) (Morgenthaler et al. 2007), with EDS and cataplexy being the most common symptoms.

Although the majority of adult patients with narcolepsy had symptoms develop before 15 years of age—in rare cases before 5 years of age—there are no approved treatments for pediatric narcolepsy/cataplexy (Dauvilliers et al. 2001, Okun et al. 2002, Yoss & Daly 1960), although all treatments used for the treatment of adults are used to treat children with narcolepsy (Mignot 2012). Modafinil, a commonly used treatment for adult narcolepsy, is not approved in children because of safety concerns related to Stevens-Johnson syndrome and, per the US product label and the EU summary of product characteristics (SmPC), should not be used for any pediatric indication (Provigil US prescribing information (PI) 2010; Provigil SmPC 2012). Dextroamphetamine is the only medication that provides dosing information for pediatric narcolepsy (Dexedrine Spansules® US PI 2010); however, it is not approved for the treatment of narcolepsy for children or adolescents in Europe. Other stimulants, which are often used for the treatment of EDS, and antidepressants, which are often used for cataplexy, may provide insufficient benefit and are associated with known risks. Clearly a need exists for safe and effective treatments for pediatric patients with narcolepsy/cataplexy.

The detrimental effects of narcolepsy on daily functioning and activities, psychosocial functioning, quality of life, and work performance—as well as effects on personal and public safety, given the increased risk of automotive and equipment accidents—are well described in the literature on adult patients (Broughton et al. 1981, Ingravallo et al. 2012). The effects of narcolepsy on the lives of pediatric patients (children and adolescents younger than 18 years of age) are less commonly described but equally burdensome. Pediatric narcolepsy is associated with limitations on children's activities due to EDS and cataplexy, poor

performance in school (after symptom onset) and difficulty with peers (Stores et al. 2006, Peraita-Adrados et al. 2011, Aran et al. 2010) and a variety of psychiatric and medical comorbidities including depression (Stores et al. 2006, Peraita-Adrados et al. 2011, Aran et al. 2010, Partinen et al. 2012), obesity (Peraita-Adrados et al. 2011, Poli et al. 2013), and precocious puberty (Peraita-Adrados et al. 2011, Poli et al. 2013).

Xyrem has been used to treat narcolepsy symptoms in children and adolescents. Data from published studies in pediatric and adult patients indicate a similar safety profile and therapeutic response to Xyrem in the two age groups (<18 and ≥18 years). Post marketing data from nearly 1,500 pediatric patients treated with Xyrem also suggest a similar safety profile in the two age groups, although some non-serious events are reported more commonly in pediatric patients than in adults, and vice versa.

Jazz Pharmaceuticals is conducting this clinical study with Xyrem in pediatric patients with narcolepsy with cataplexy to generate efficacy, safety, and pharmacokinetics (PK) information on Xyrem in the pediatric population.

## 1.1 Background and Rationale

This study is being conducted under the US Food and Drug Administration's (FDA) pediatric Written Request.

On February 24, 2016, the Data and Safety Monitoring Board (DSMB) for this study reviewed the results from a pre-planned interim analysis of the primary efficacy results based on 35 subjects having completed or discontinued from the Double-blind Randomized Withdrawal Period of the protocol. The result of this analysis demonstrated positive efficacy on the primary endpoint, the change in weekly number of cataplexy attacks from the last 2 weeks of the Stable-Dose Period to the 2 weeks of the Double-Blind Treatment Period at a significance level of  $p < 0.005$ . Based on this analysis, the DSMB recommended that the placebo treatment in the Double-Blind Withdrawal Period of the trial be stopped and the open-label portion of the study be continued, so as not to expose further subjects to placebo treatment. Amendment 4 to this protocol was based on that recommendation. The current amendment (Amendment 5) provides subjects who have completed one year in the study (Part 1) the opportunity to continue treatment for up to an additional 2 years or until they reach 18 years of age or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first.

### 1.1.1 Clinical Experience

#### 1.1.1.1 Adult Studies

The effectiveness of Xyrem in treating the two main symptoms of narcolepsy—EDS and cataplexy—in adult subjects was demonstrated in three controlled clinical trials with 611 patients with narcolepsy (398 subjects treated with Xyrem). Adverse events seen with frequencies of ≥5% and twice the rate of placebo in Xyrem-treated patients were nausea (20.9%), dizziness (19.7%), vomiting (8.5%), enuresis (6.5%), and diarrhea (5%). Xyrem was also evaluated in one Phase 2 and two Phase 3 randomized, controlled clinical trials in patients with fibromyalgia; however, Xyrem is not approved for fibromyalgia. Results of those studies indicate a similar safety profile to that seen in clinical trials for narcolepsy

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(Moldofsky et al. 2010, Russell et al. 2011, Spaeth et al. 2012, Spaeth et al. 2013). A study in patients with moderate to severe sleep apnea was conducted as a post marketing commitment (requirement). Xyrem treatment was not associated with an increase in apnea hypopnea index (AHI) but some clinically significant desaturations were observed (George et al. 2010).

The PK of Xyrem was extensively characterized in the clinical program that supported use of this drug for the indications of EDS and cataplexy in patients with narcolepsy. Xyrem is eliminated almost exclusively by metabolism through the Krebs cycle and does not inhibit CYP enzymes (Xyrem US PI 2016). Following oral administration, Xyrem is absorbed rapidly and consistently across the clinical dose range, with an absolute bioavailability of about 88%. The average peak concentrations ( $C_{max}$ ) following administration of each of two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration ( $T_{max}$ ) ranged from 0.5 to 1.25 hours. Following oral administration, the plasma concentrations of sodium oxybate increased more than dose-proportionally, with blood levels increasing 3.7-fold as the total daily dose is doubled from 4.5 to 9 g.

#### 1.1.1.2 Pediatric Studies

##### **EFFICACY DATA IN THE LITERATURE**

The effectiveness of Xyrem in pediatric patients with narcolepsy/cataplexy has been described in five published studies: one controlled study and four published retrospective case analyses, with a combined total of 100 patients (Murali & Kotagal 2006, Aran et al. 2010, Lecendreux et al. 2012, Mansukhani & Kotagal 2012, Huang & Guilleminault 2009). Overall, Xyrem was shown to be effective in treating the symptoms of cataplexy, EDS, and DNS in narcolepsy in the scientific literature reporting its effects in children and adolescents.

##### **SAFETY DATA IN THE LITERATURE**

Safety data from Xyrem in children and adolescents with narcolepsy/cataplexy were reported in six published studies: four retrospective case analyses and two prospective studies, with a combined total of 109 patients who took Xyrem for 2 to 90 months (Murali & Kotagal 2006, Aran et al. 2010, Lecendreux et al. 2012, Mansukhani & Kotagal 2012, Huang & Guilleminault 2009, Poli et al. 2012). The safety profile of Xyrem in children and adolescents as reported in the scientific literature is similar to the known safety profile of Xyrem in adults.

Adverse events reported in these six studies were similar to those seen with adults. Adverse events reported by more than 10% of patients in any one study were as follows: weight loss, headache, nausea, DNS, irritability, parasomnias, dry mouth, increased awakenings, dizziness, terminal insomnia, groaning, and sleepiness. There were no reports of premature puberty in 11 pre-pubertal children taking Xyrem (Aran et al. 2010) or adverse effects on growth parameters including weight, height, and body mass index (BMI) in a study of 15 children and adolescents (Mansukhani & Kotagal 2012). In these publications, the most serious AEs were increased nightmares and suicidal ideation and gesture in a 9-year-old patient (Murali & Kotagal 2006).

Reasons for discontinuations across the six studies included increased nightmares and suicidal ideation, dissociative feelings, and problems receiving drug shipments (Murali & Kotagal 2006); AEs (not specified) in 18% of pre-pubertal patients, lack of efficacy in 15%

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of peri- or post-pubertal patients, and cost of drug in 5% to 6% of all patients (Aran et al. 2010); sleep loss and persistent nausea, each in 2 of 27 (7%) patients (Lecendreux et al. 2012); nausea, constipation and dissociative feelings in 1 of 15 (7%) patients, and body aches and dizziness in 1 of 15 (7%) patients who later resumed use of the drug (Mansukhani & Kotagal 2012); and nausea in 1 of 9 (11%) patients (Poli et al. 2012). Huang & Guillemineault (2009) did not report discontinuations. These reasons for discontinuation are common in adult patients as well.

#### **PHARMACOKINETIC DATA**

There are no PK data on Xyrem in children under 18 years of age. Although there are no studies examining the PK of sodium oxybate in children, it is known that the gastrointestinal system, which may have direct consequences on absorption bioavailability, clearance, and biotransformation of drugs, is functionally mature by about 1 year of age (Walthall et al. 2005). Intravenous GHB has been used and studied in children at doses of 25 to 50 mg/kg (Rousseau et al. 2012) and up to 90 mg/kg for sedation (Meyer et al. 2003); and at doses up to 100 mg/kg for anesthesia (Hunter et al. 1971). The central nervous system (CNS) effects were consistent with those obtained with intravenous GHB in adults (Kleinschmidt & Mertzluft 1995, Solway & Sadove 1965), suggesting that post-absorption PK and pharmacodynamics are similar in children and adults.

#### **1.1.2 Postmarketing Safety Data: 2002 through September 30, 2012**

A total of 43,306 US patients have received at least one shipment of Xyrem from product launch in 2002 through September 30, 2012. Of those, approximately 1,500 patients began Xyrem treatment when they were younger than 18 years old, totaling approximately 1,150 patient-years of exposure in pediatric patients, with a duration of use up to 7.4 years. Overall, the safety profile for frequent AEs reported in pediatric patients on Xyrem is similar to that seen with adults, with nausea, vomiting, dizziness, headache, somnolence, insomnia, and fatigue among the most common AEs in both patient populations. Enuresis, somnambulism, drug dose omission, nasopharyngitis, drug ineffective, and cataplexy were among the most frequently reported AEs in pediatric patients but these AEs were not as commonly reported in adults. Most of these common pediatric AEs are typically not considered to be serious, and some are related to childhood development and/or the underlying disease. Enuresis, for example, is a typical childhood disorder, and Xyrem likely contributes to its re-emergence by promoting deep sleep.

Three deaths were reported in children who had received Xyrem treatment: one case of aspiration pneumonia in a 3-year-old boy with substantial developmental issues, one unconfirmed cause of death in an 11-year-old girl with reported cancer pain, and one homicide victim who was a 16-year-old girl. There is no evidence that Xyrem was abused or misused by pediatric patients prescribed Xyrem, although medication errors, primarily from misunderstanding dosing instructions and abuse in one pediatric case associated with drug diversion from a patient, did occur. There is no signal that pediatric patients are more prone than adult patients taking Xyrem to depression, anxiety, convulsion, depressed level of consciousness, impaired respiratory drive, or psychiatric problems. No completed suicide was reported in pediatric patients. Suicidal ideation was coded in 5 pediatric patients, and suicide attempt was coded in 4 patients (all of whom were 16 or 17 years old); 3 of the

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4 patients had a history of depression or bipolar disorder. Of these 4 patients, 2 used antiepileptic drugs, 2 used SSRIs, and one used an antidepressant (Xyrem IB).

### 1.1.3 Drug-Drug Interaction

Several drug-drug interaction studies in healthy volunteers (Xyrem with zolpidem, protriptyline, modafinil, omeprazole, duloxetine, tramadol, lorazepam, ibuprofen, diclofenac, and divalproex sodium) were conducted to evaluate the effects of co-administration of medications likely to be used concomitantly with Xyrem. There were no significant PK or pharmacodynamic (PD) interactions between Xyrem and zolpidem, protriptyline, modafinil, omeprazole, duloxetine, tramadol, lorazepam, or ibuprofen.

- Co-administration of Xyrem with diclofenac showed no significant differences in plasma PK or renal excretion of sodium oxybate, and it did not appear to affect the PK of diclofenac. However, PD interactions, including reduced impairments to attention, were observed in the co-administration of Xyrem with diclofenac.
- Co-administration of Xyrem with divalproex sodium resulted in an increase in AUC and an increase in renal clearance of sodium oxybate;  $C_{max}$  was unchanged. It did not appear to affect the PK of valproic acid. Pharmacodynamic interactions were also observed following co-administration; these included increased impairment to cognitive function and increased sleepiness.

Among adverse events (AEs) occurring in at least 2 healthy subjects in any treatment group in these studies, the following AEs were seen more frequently with co-administration than with Xyrem alone:

- Zolpidem: dizziness
- Protriptyline: dizziness
- Modafinil: headache, vomiting, emotional lability
- Omeprazole: vomiting, stupor
- Duloxetine: somnolence, depressed mood
- Tramadol: somnolence, nausea, dizziness, abdominal pain, vomiting
- Lorazepam: somnolence, nausea, dizziness, vomiting
- Ibuprofen: dizziness, headache, euphoric mood
- Diclofenac: dry mouth, feeling hot, somnolence, euphoric mood
- Divalproex sodium: nausea, somnolence, euphoric mood.

## 2 STUDY OBJECTIVES

### 2.1 Objectives

Primary objectives are:

1. To evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy

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2. To evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to one year (and potentially more than one year in some subjects participating in a continuation of the open-label safety evaluation)

Secondary objectives are:

1. To evaluate the efficacy of Xyrem in the treatment of excessive daytime sleepiness (EDS) in pediatric subjects with narcolepsy with cataplexy
2. To characterize the pharmacokinetics (PK) of Xyrem in pediatric subjects (ages 7-17 years) with narcolepsy with cataplexy
3. To evaluate the safety of titrating Xyrem in pediatric subjects to an effective and tolerable dose

### 3 INVESTIGATIONAL PLAN

#### 3.1 Overall Study Design and Plan

Under Amendment 5, this study is divided into two parts: Part 1 includes one year of treatment, and Part 2, the Open-Label Continuation Period, provides the opportunity to continue treatment for up to an additional 2 years.

Part 1 of this study was initially designed as a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution. As a result of a preplanned interim analysis, which demonstrated positive efficacy results on the primary efficacy endpoint, the protocol was amended (Amendment 4) to replace the placebo treatment in the Double-Blind Treatment Period with open-label Xyrem treatment. After Amendment 4 becoming effective, all subjects entering the Double-Blind Treatment Period will receive open-label Xyrem treatment. For administrative reasons, the term “Double-Blind Treatment Period” will continue to be used throughout the protocol. Following the Double-Blind Treatment Period (2 weeks), Part 1 includes an open-label safety extension allowing subjects to continue Xyrem treatment for up to one year. In addition, the PK of Xyrem will be evaluated in a subset of subjects in Part 1.

Part 2 is an open-label continuation period, to provide continued access to Xyrem to subjects who have completed one year in the study and to monitor the long-term safety of Xyrem. Upon approval of Amendment 5, subjects who complete one year in the study (Part 1) may continue in Part 2, which will provide up to 2 years of additional treatment. Subjects who have already completed Part 1 prior to Amendment 5 may re-enroll in Part 2. Subjects will have the opportunity to continue open-label Xyrem treatment in Part 2 until the first occurrence of any of the following:

- Up to an additional 2 years
- Until the subject reaches 18 years of age
- Until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI)

Children and adolescents, diagnosed with narcolepsy with cataplexy who are currently treated with Xyrem or are Xyrem naïve, with or without concomitant stable stimulant use, are eligible to enter the study. For this study, a Xyrem-naïve subject is defined as a subject who

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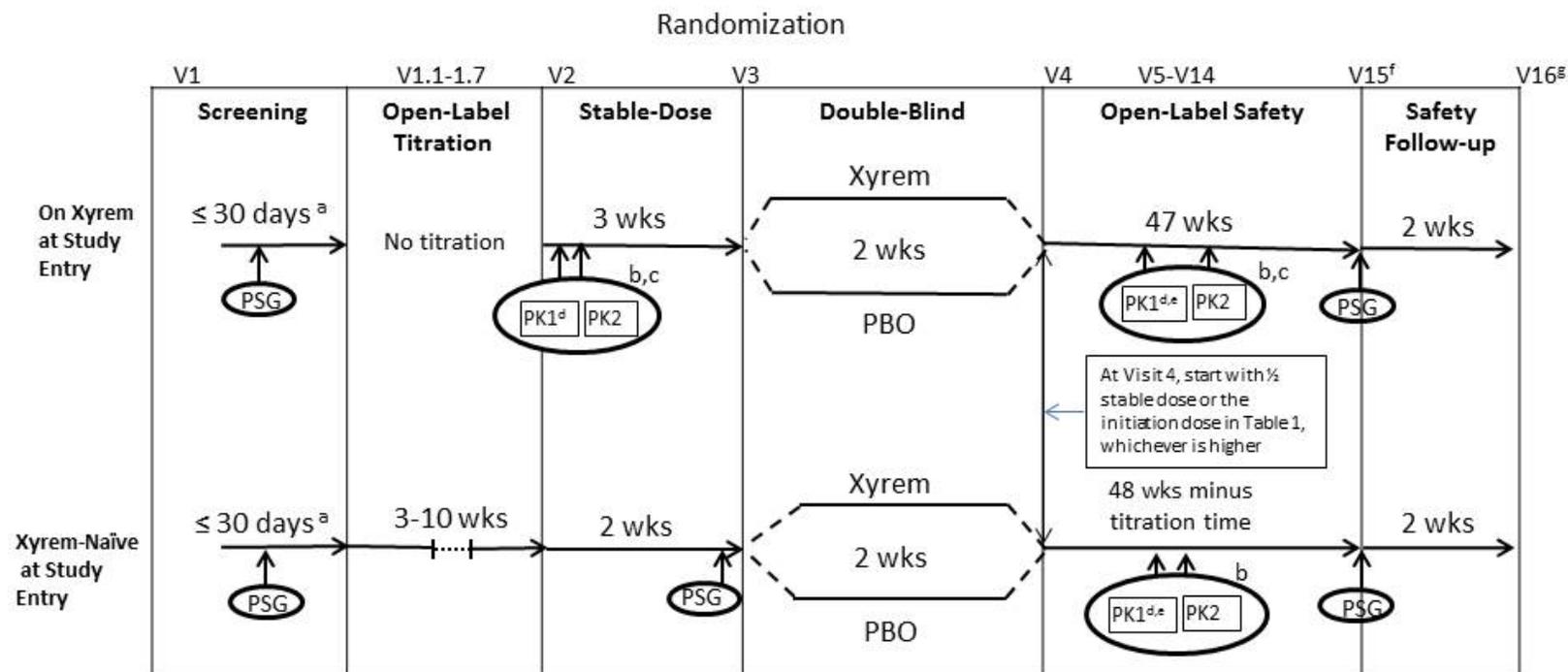
has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Part 1 Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

[Figure 1](#) presents the study schema for subjects who entered the Double-Blind Period prior to Amendment 4 becoming effective and [Figure 2](#) presents the study schema for subjects entering the Double-Blind Period after Amendment 4 becoming effective. [Figure 3](#) presents the study schema for Part 2 of the study. Schedules of events for Part 1 are in [Appendix 1](#) and [Appendix 2](#) for subjects on Xyrem at study entry and Xyrem-naïve subjects, respectively. Schedules of events for Part 2 are in [Appendix 22](#) for subjects continuing directly from Part 1, [Appendix 23](#) for subjects re-enrolling who do not require titration, and [Appendix 24](#) for subjects re-enrolling who require titration.

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**Figure 1 Part 1 Study Schema –for subjects entered in the Double-Blind Period prior to Amendment 4 becoming effective**



<sup>a</sup> Up to 30 days. If needed, additional time may be granted with permission of the medical monitor.

<sup>b</sup> PK Nights 1 and 2 are only for the subset of subjects who have provided assent/consent to participate in the PK evaluation.

<sup>c</sup> Either in Stable-Dose or Open-Label Safety Period.

<sup>d</sup> 1/2 of usual nightly dose. Doses must match the printed gradations (lines) on the dosing syringe. See [Section 3.1.7](#).

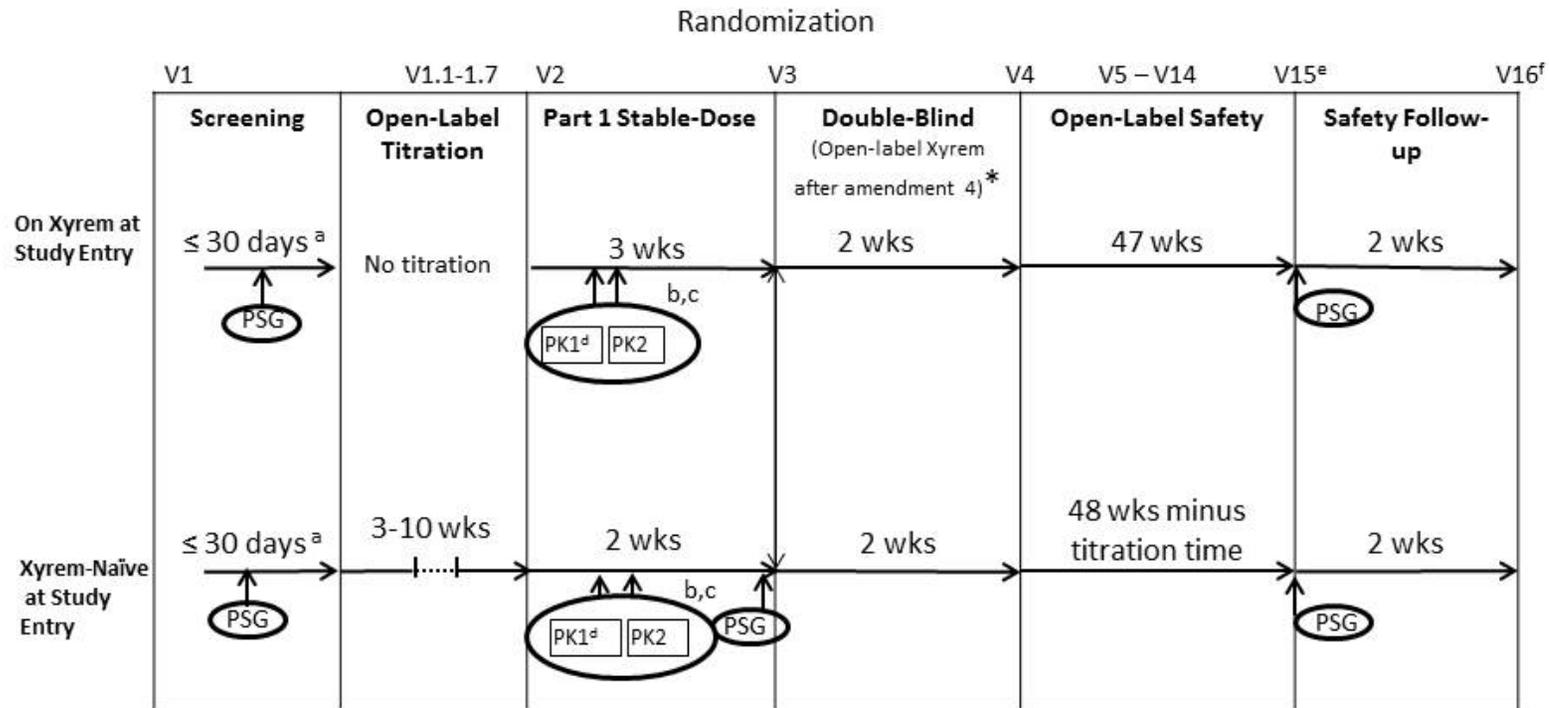
<sup>e</sup> Once the subject is titrated and on a stable dose of Xyrem.

<sup>f</sup> If subject is continuing into Part 2, see [Appendix 22](#).

<sup>g</sup> No safety follow-up period for subjects who continue directly into Part 2.

PBO = placebo; PSG = polysomnography; V = visit; wks = weeks

**Figure 2 Part 1 Study Schema –for subjects entering the Double-Blind Period after Amendment 4 becoming effective**



\* Subjects entering the Double-Blind Period after Amendment 4 becomes effective will receive open-label Xyrem during this period.

<sup>a</sup> Up to 30 days. If needed, additional time may be granted with permission of the Medical Monitor.

<sup>b</sup> PK Nights 1 and 2 are only for the subset of subjects who have provided assent/consent to participate in the PK evaluation.

<sup>c</sup> Conduct PK procedures at any time from Stable-Dose Period on after the subject has reached a stable dose of Xyrem.

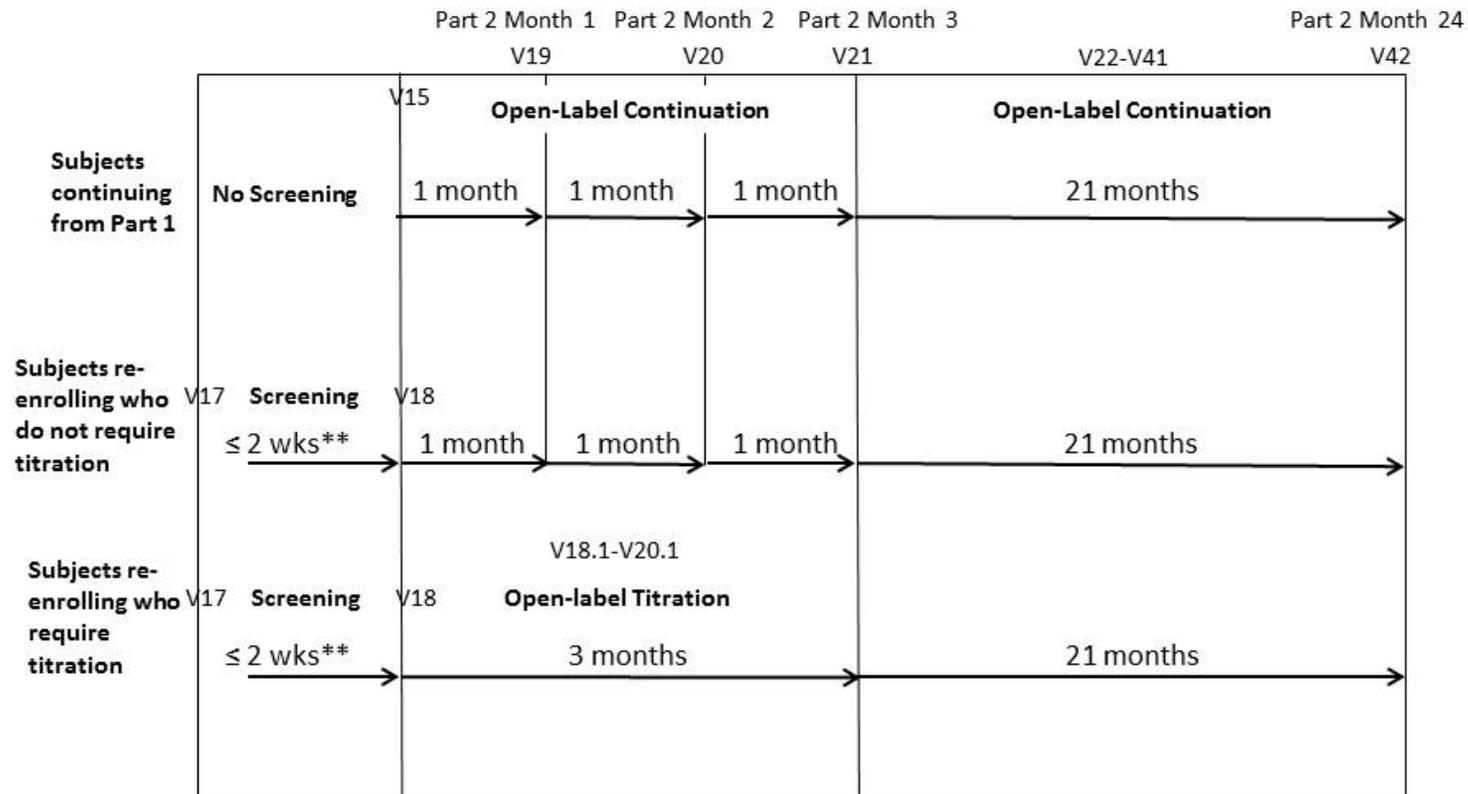
<sup>d</sup> ½ of usual nightly dose. Doses must match the printed gradations (lines) on the dosing syringe. See Section 3.1.7.

<sup>e</sup> If subject is continuing into Part 2, see Appendix 22.

<sup>f</sup> No safety follow-up period for subjects who continue directly into Part 2.

PSG = polysomnography; V = visit; wks = weeks

**Figure 3 Part 2 Study Schema\***



\* Subjects may participate in Part 2 for up to an additional 2 years, until they reach 18 years of age, or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information, whichever occurs first.

\*\* Up to 2 weeks. If needed, additional time may be granted with permission of the medical monitor.

V = visit; wks = weeks

### 3.1.1 Screening Period

#### Part 1 Screening

All subjects will be evaluated for eligibility during a Screening Period of up to 30 days. If needed, additional screening time may be granted with permission of the Medical Monitor. However, if it has been more than 45 days since the Screening safety labs pertinent to eligibility were drawn, these labs may need to be repeated as instructed by the Medical Monitor. Eligibility screening will be performed prior to the Xyrem Open-Label Titration for Xyrem-naïve subjects or prior to the open-label Stable-Dose Period for subjects already taking a stable dose of Xyrem and whose cataplexy symptoms are stable.

All subjects who are eligible for Part 1 of the study must be evaluated by polysomnography (PSG) for sleep-disordered breathing during the Part 1 Screening Period.

Blood volumes drawn during the study should not exceed the amounts recommended in the guidance from Seattle Children's Hospital ([Appendix 4](#)), European Union (EU) Guidelines (2008), or other local regulations. Therefore, for those subjects on Xyrem at study entry who have low body weight and are participating in the PK evaluation during the Stable Dose Period, it is recommended that the screening blood draw be performed at the beginning of the Part 1 Screening Period and that the Part 1 Screening Period be as close as possible to 30 days to minimize the amount of blood drawn over 30 days.

#### Part 2 Screening

All subjects who complete Part 1 of the study are eligible to participate in Part 2. Subjects who re-enroll after completing Part 1 of the study must complete the Part 2 Screening. Part 2 Screening will occur within 2 weeks before the first drug-dispensing visit; however, additional screening time may be granted with permission of the Medical Monitor, if needed. Subjects re-enrolling in Part 2 within 2 weeks of Visit 15 will not require clinical laboratory tests, urine drug screening, an alcohol test, or a serum pregnancy test at the Part 2 Screening visit (Visit 17). For these subjects, Visit 17 and the first drug-dispensing visit (Visit 18) may occur on the same day.

### 3.1.2 Open-Label Titration Period for Subjects who are Xyrem naïve (up to 10 weeks)

For subjects who are Xyrem naïve or who re-enroll in Part 2 and require titration (i.e., have been off Xyrem for  $\geq 1$  month), Xyrem therapy will be initiated based on the subjects' weight as specified in [Table 1](#). Xyrem doses are administered in two equally divided doses (see [Section 5.3](#)).

Subjects will be titrated on Xyrem to achieve a maximum clinical benefit in cataplexy and EDS while maintaining tolerability. Dose adjustment during the Part 1 Open-Label Titration Period and Part 2 Open-Label Titration will proceed based on the subject's weight to a dose level no higher than the maximum dose described in [Table 1](#) in 10 weeks. The study drug titration rate is  $\leq 1$  g/night/week for subjects  $< 45$  kg, and  $\leq 1.5$  g/night/week for subjects  $\geq 45$  kg ([Table 1](#)). Each dose must match a printed line on the dosing syringe ([Figure 4](#)). Once the Xyrem dose has been optimized per the Investigator's judgment, the subject may enter the open-label Stable-Dose Period (for Part 1) or continue in the Open-Label Continuation (for Part 2) with that dose.

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**Table 1 Xyrem Dose Initiation and Titration for Xyrem-naïve Subjects**

Subject weight	Initiation dose (taken in two equally divided doses)*	Titration regimen	Maximum total nightly dose
<30 kg	≤2 g/night	≤1 g/night/week	6 g/night
≥30 kg – <45 kg	≤3 g/night	≤1 g/night/week	7.5 g/night
≥45 kg	≤4.5 g/night	≤1.5 g/night/week	9 g/night

\*At bedtime and 2.5 to 4 hours later. For children who sleep more than 8 hours per night, Xyrem may be given after bedtime, while the child is in bed, in two equally divided doses 2.5 to 4 hours apart.

Xyrem dose reduction is allowed for tolerability reasons at any time, at the Investigator's discretion, in any decrement that is a multiple of 0.5 g/night. Stimulant taper and withdrawal may be attempted at the Investigator's discretion during the Open-Label Titration Period.

### 3.1.3 Open-Label Stable-Dose (Stable-Dose) Period (2-3 weeks)

#### 3.1.3.1 For Subjects on Xyrem at Study Entry

Subjects who have been titrated to a stable dose of Xyrem prior to study entry will remain on the stable dose and regimen (i.e., two equally divided doses or two unequally divided doses) of Xyrem, and a stable stimulant dose if applicable, for 3 weeks with the exception of PK nights (if applicable) (see [Section 3.1.7](#)). During the first week of this 3-week period, subjects and/or parent(s)/guardian(s) will become familiar with methods of recording efficacy and safety data.

#### 3.1.3.2 For Xyrem-naïve Subjects

Xyrem-naïve subjects who have been titrated to an optimal Xyrem dose and a stimulant dose (if applicable), during the Open-Label Titration Period, will remain on the dose that is established at the end of the Open-Label Titration Period for 2 weeks during the Stable-Dose Period. Subjects and/or parent(s)/guardian(s) will become familiar with the methods of recording efficacy and safety data during the Open-Label Titration Period.

On the last night of the Stable-Dose Period, Xyrem-naïve subjects will be assessed by PSG while taking Xyrem (End of Stable-Dose/Pre-Randomization PSG Night). [Note: Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will not be randomized, however, for administrative reasons the terminology for this PSG will retain the reference to "Pre-Randomization".]

### 3.1.4 Double-Blind Treatment Period (2 weeks)

#### 3.1.4.1 Subjects entering the Double-Blind Treatment (Randomized Withdrawal) Period prior to Amendment 4 becoming effective

Subjects had been randomized 1:1 to one of the following two treatment groups at the end of the Stable-Dose Period (Visit 3).

1. **Xyrem:** Active Xyrem will be continued as a double-blind treatment at the stable dose taken and regimen used in the prior 2 weeks

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2. **Placebo:** Xyrem placebo will be initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

During the Double-Blind Period, subjects will remain on the same dosing regimen they used during the Stable-Dose Period, with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart. For subjects on concomitant stimulant therapy, subjects will remain on the same stable stimulant dose as at the end of the Stable-Dose Period during the Double-Blind Treatment Period.

Subjects who complete the entire 2-week Double-Blind Treatment Period will be eligible to continue in the open-label Xyrem safety evaluation.

3.1.4.2 Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective

Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment during this period.

3.1.5 Open-Label Safety Period (to allow up to 1 year Xyrem exposure)

Subjects who are eligible to participate in the Open-Label Safety Period will participate in this period for 47 weeks if they entered the study on a stable dose of Xyrem or for a period of 38-45 weeks if they entered as Xyrem naïve, depending on the duration of the titration period in which they participated (45 weeks assumes that the shortest titration period will be 3 weeks for those subjects who reach an optimal response very quickly during titration).

All study procedures and assessments will be carried out according to the planned schedule (changes in Xyrem dose will generally not affect the schedule).

All subjects will be seen in the clinic 4 weeks after the Open-Label Safety Period begins (Visit 5) and then at Weeks 18, 26, 39, and 52 from study entry (Day 1). However, if in the case of subjects who are Xyrem naïve, Visit 5 is within 2 weeks of the Week 18 visit, the first clinic visit of the Open-Label Safety Period will be the Week 18 visit.

Subjects/parent(s)/guardian(s) will be contacted in the interim by phone at Weeks 16, 22, 30, 34, 43, and 48 from study entry (Day 1). A final PSG will be performed at Week 52 or the Part 1 early termination visit (if the subject who terminates early is willing to participate in another PSG night and if they are willing to take Xyrem the evening of the PSG). The Part 1 early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period. Clinicians may schedule clinic or phone visits between protocol-specified clinic visits to ensure subject safety or to accommodate PK visits (if applicable). Additional drug dispensing visits may be added as required by local law or at the Investigator's discretion based on safe drug storage requirements. Stimulants for EDS may be used as adjunctive therapy throughout the trial, and can be adjusted or discontinued as appropriate.

For subjects who had entered the Double-Blind Treatment Period before Amendment 4 was effective, upon entering the Open-Label Safety Period, these subjects will be started at a dose no higher than half the Xyrem dose they received at the end of the Stable-Dose Period or the

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initiation dose defined in [Table 1](#), whichever is higher. Subjects will then be titrated up to their optimal dose as tolerated according to the Investigator's judgment (the maximum dose should not exceed the doses defined in [Table 1](#) or the stable dose prior to study entry, whichever is higher, and should not be greater than 9 g/night). Xyrem dose up-titration is allowed at no more than 1.5 g/night, and during dose up titration the Investigator must monitor tolerability, which includes AEs observed at night, such as confusion, respiratory depression, sleepwalking and other parasomnias; residual effect and AEs observed during daytime, such as confusion, somnolence, pronounced levels of depressed consciousness, depressed mood and suicidality, anxiety, abuse or misuse of Xyrem, and weight loss.

Subjects may take two equally divided doses or two unequally divided doses with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart. Xyrem dose adjustment due to tolerability and efficacy is permitted. Only doses that match the printed gradations (lines) on the dosing syringe are permitted.

### 3.1.6 Safety Follow-up Visit (2 weeks post Part 1 termination)

If a subject does not complete Part 1 of the study or does not immediately continue into Part 2, a safety follow-up visit will be conducted 2 weeks following the Part 1 termination visit.

After participation in Part 1 of the study, subjects will have received up to 12 months (52 weeks) active treatment. The duration of Part 1 is at most 54 weeks, including the 2-week post-study period before the safety follow-up visit. Subjects will not be given study drug during this 2-week period but are expected to be treated for their cataplexy and EDS with any commercially available medications as appropriate during this time by their treating physicians.

See [Appendix 1](#) and [Appendix 2](#) for the Schedules of Events.

### 3.1.7 Open-Label PK Evaluation

At certain study sites during Part 1, eligible subjects will additionally participate in the PK evaluation. Subjects will be stratified to two age groups: 7-11 years of age and 12-17 years of age. Up to 18 subjects in each of the two age groups will be eligible to participate in the PK evaluation. Every effort will be made to ensure a minimum of 12 subjects in each age group complete the PK assessments. If the variability of PK data in children and adolescents is comparable to that of adults, a sample size of 12 completers in each age group is expected to provide adequate precision to characterize the PK of sodium oxybate in each age group. However, when sufficient data are obtained to characterize the PK profile with adequate precision during the study, as determined by the Data and Safety Monitoring Board, or when enrollment of 100 subjects in the study has been reached, enrollment in the PK evaluation will stop and existing data will be analyzed and reported.

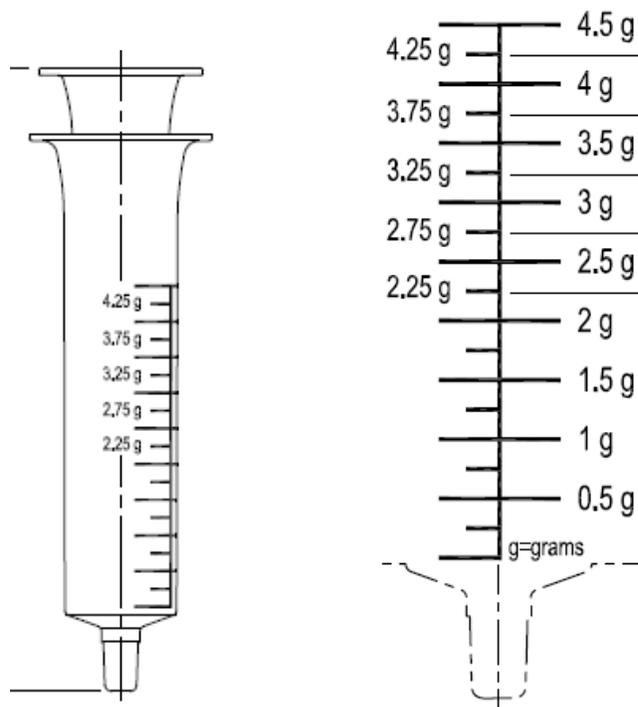
Eligible subjects will spend two nights in the clinic for the PK evaluation (PK Nights 1 and 2). PK evaluation will occur at any time while subjects are on a stable dose of Xyrem. On PK Night 1, subjects will receive one half of their usual and current total nightly Xyrem dose (administered as two equally divided doses, given while in bed at bedtime and 4 hours later). Subjects will return to the clinic for PK Night 2 and will receive Xyrem at their stable, usual dose (administered as two equally divided doses, given while in bed at bedtime and

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4 hours later). Each divided dose must match a printed gradation (line) on the dosing syringe; therefore, if a dose cannot be measured using the lines on the dosing syringe, the dose should be decreased to the next lower printed line on the dosing syringe. For example, if a subject is supposed to take a total dose of 4.25 g on a PK night, then the two equally divided doses would be 2.125 g each. There is no printed line for 2.125 g on the dosing syringe. The next lower line on the syringe would be 2 g (see Figure 4). The subject would then take the two equally divided doses of 2 g each, which would equal a total nightly dose of 4 g. The actual doses taken will be recorded on the CRF.

**Figure 4 Example Dosing Syringe and Gradations (lines)**



A limited number of blood samples will be taken to measure sodium oxybate concentrations on each of these PK nights. Samples will be taken relative to the first nightly Xyrem dose at 0 (pre-dose), 0.75, 1.5, 2.5, and 4 hours (pre-2nd dose), to characterize the PK of the first dose of Xyrem, and two samples will be taken to characterize the peak and residual exposure associated with the second dose, at 4.75 and 8 hours after the first dose of Xyrem (total blood volume required for PK samples is 40 mL taken over a minimum of 2 days). Following the PK nights, subjects will resume their usual Xyrem dose and regimen and their stimulant dose, if applicable.

Subjects taking two unequally divided doses are eligible to participate in the PK evaluation if the subjects are willing to take two equally divided doses 4 hours apart on PK nights. The equally divided doses for these subjects must also match the printed lines on the dosing syringe (see above).

Subjects in the PK evaluation will also undergo all other Part 1 study procedures specified in the protocol.

### 3.1.8 Open-Label Continuation Period (Part 2)

Upon approval of Amendment 5, subjects who have completed Part 1 in the study may participate in Part 2 of the study. Subjects ongoing in the study when Amendment 5 becomes effective may enter Part 2 after completing the Part 1 Open-Label Safety Period, bypassing the 2-week Safety Follow-up Period. These subjects will begin Part 2 at Visit 15. Subjects who have already completed Part 1 of the study may re-enroll in Part 2. Subjects who re-enroll must complete the Part 2 Screening Visit. Subjects must be on a stable dose of Xyrem, or if they have been off Xyrem for  $\geq 1$  month, must be titrated to an effective and tolerable Xyrem dose. For subjects who have been off Xyrem for less than 1 month, titration may also be required per the Investigator's judgment. Subjects will be titrated to Xyrem as described in [Section 3.1.2](#). In Part 2, subjects will have the opportunity to continue open-label Xyrem treatment until the first occurrence of any of the following:

- Up to an additional 2 years
- Until the subject reaches 18 years of age
- Until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI)

Safety will be assessed at scheduled visits throughout Part 2. All subjects will be seen in the clinic at the beginning of Part 2 (Visit 15 for subjects continuing and Visits 17 and 18 for subjects re-enrolling) and every 3 months thereafter. Subjects/parent(s)/guardian(s) will be contacted in the interim months by phone. Clinicians may schedule clinic or phone visits between protocol-specified clinic visits to ensure subject safety. Additional drug dispensing visits may be added as required by local law or at the Investigator's discretion based on safe drug storage requirements. For subjects turning 18 years of age, the Part 2 Study Termination visit must be scheduled prior to the subject's 18<sup>th</sup> birthday.

Subjects who re-enroll and require titration in Part 2 will be titrated on Xyrem to achieve clinical benefit in cataplexy and EDS while maintaining tolerability based on the Investigator's assessment. Following Visit 18 (begin titration), the subject/parent(s)/guardian(s) will be contacted by phone at titration weeks T2, T3, T4, T7, T8, and T10 to determine if additional titration is necessary or to follow up after the subject has reached a stable dose.

## 3.2 Rationale for Study Design and Control Group

A double-blind placebo controlled randomized-withdrawal study of Xyrem in adult narcolepsy patients, OMC-SXB-21, was one of the pivotal studies that supported FDA approval of Xyrem for the treatment of cataplexy and EDS in patients with narcolepsy. This study design ensures that all subjects are able to receive Xyrem treatment and minimizes the duration of placebo exposure. This study is being conducted under FDA's pediatric Written Request, in which the Agency requested a double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of sodium oxybate, combined with an open-label evaluation of the pharmacokinetics of sodium oxybate, and an open-label

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safety evaluation with combined time of sodium oxybate treatment of up to one year (and potentially more than one year in some subjects participating in a continuation of the open-label safety evaluation) in pediatric patients who have narcolepsy with cataplexy. Placebo is the only control group used in this study, there are no other medications approved for the treatment of cataplexy. In this study, the maximal time that any pediatric subject will be exposed to placebo is 2 weeks.

As a result of a preplanned interim analysis, which demonstrated positive efficacy results on the primary efficacy endpoint, the protocol has been amended (Amendment 4) to replace placebo treatment in the Double-Blind Treatment Period with open-label Xyrem treatment. After Amendment 4 becoming effective, all subjects entering the Double-Blind Treatment Period will receive open-label Xyrem treatment during this period.

Part 2 is an open-label continuation period, to provide continued access to Xyrem to subjects who have completed one year in the study and to monitor the long-term safety of Xyrem.

### **3.3 Study Duration**

It is anticipated that enrollment in Part 1 will be completed within 2 years. Following the Part 1 Screening Period of up to 30 days (if needed, additional time may be granted with permission of the Medical Monitor), the expected duration of study participation for each subject in Part 1 will be approximately 54 weeks, including a 2-week safety follow-up period. Under Amendment 5, subjects may continue on in Part 2, the Open-Label Continuation Period, after 52 weeks in Part 1, bypassing the 2-week Safety Follow-up Period, or they may re-enroll in Part 2 after completing Part 1. Subjects may participate in Part 2 for up to an additional 2 years or until they reach 18 years of age or for up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first. Therefore, a subject's duration of participation in Part 2 will be up to 2 years.

## **4 STUDY POPULATION SELECTION**

### **4.1 Study Population**

The study will enroll pediatric subjects who are diagnosed with narcolepsy with cataplexy, who have provided assent, and whose parent(s) or guardian(s) have signed the informed consent form in accordance with local IRB/IEC requirements. At least 100 subjects will be enrolled in the study. Every effort will be made to enroll approximately 30 subjects on Xyrem at study entry of the anticipated 100 subjects enrolled. Other subjects enrolled will be Xyrem naïve at study entry.

A subset of the subjects who are taking Xyrem at a stable dose for their narcolepsy symptoms will participate in the PK evaluation during Part 1. Up to 18 subjects in each of the two age groups (7-11 year olds and 12-17 year olds) will be enrolled. Every effort will be made to ensure a minimum of 12 subjects in each age group complete the PK assessments. However, when sufficient data are obtained to characterize the PK profile with adequate precision during the study, as determined by the Data and Safety Monitoring Board, or when

enrollment of 100 subjects in the study has been reached, enrollment in the PK evaluation will stop and existing data will be analyzed and reported.

## 4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in Part 1 of the study.

1. Male or female subjects aged 7-16 years at Visit 2 for subjects on Xyrem at study entry and at Visit 1.1 for Xyrem-naïve subjects (to ensure subjects are <18 years of age at the end of Part 1)
2. Have a primary diagnosis of narcolepsy with cataplexy that meets International Classification of Sleep Disorders (ICSD)-2 or ICSD-3 criteria, whichever was in effect at the time of the diagnosis or, with the permission of the Medical Monitor, completes a Multiple Sleep Latency Test (MSLT) during Screening to confirm the diagnosis of Type 1 narcolepsy by ICSD-3 criteria (i.e., the subject meets all other ICSD-3 criteria for Type 1 narcolepsy)
3. Be positive for the Human Leukocyte Antigen (HLA) DQB1:0602 haplotype, determined prior to the study or as part of the study screening procedures, or have cerebrospinal fluid (CSF) hypocretin level  $\leq 110$  pg/mL determined prior to the study. In the absence of both, be evaluated by a panel of narcolepsy experts to confirm the diagnosis of narcolepsy with cataplexy in accordance with ICSD-3
4. Have given documented assent per local IRB/IEC requirements indicating that he/she was aware of the investigational nature of the study and the required procedures and restrictions before participation in any protocol-related activities
5. Have parent(s)/guardian(s) who have given informed consent for his/her/their child's participation in the study
6. Have a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment
7. Be willing to spend the required number of nights (2 to 3) in a sleep laboratory for PSG evaluations
8. If currently treated with Xyrem, must have been taking unchanged doses (twice nightly dosing no higher than 9 g/night) of Xyrem, and stimulants, if applicable, for the treatment of narcolepsy symptoms for at least 2 months prior to screening
9. If currently treated with Xyrem, must have demonstrated clinical improvement of cataplexy per Investigator's clinical judgment
10. Have agreed to abstain from caffeinated products during PSG and PK Nights
11. Any female subject of child-bearing potential must be willing to use a method of contraception, deemed medically acceptable by the Investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination
12. Any male subject who is sexually active with a female partner must be willing to use a method of contraception, deemed medically acceptable by the Investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination

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In addition to the above inclusion criteria, prior to participating in the PK evaluation, subjects must meet the following inclusion criteria:

13. Be willing to spend 2 additional nights in the clinic for PK evaluation
14. This criterion was removed during Amendment 2
15. Have given additional documented assent and consent by the parent(s) or guardian(s) indicating awareness of the investigational nature of the PK evaluation and the required procedures and restrictions before participation in any PK-related activities
16. Have sufficient blood volume for PK sampling based on body weight in accordance with Seattle Children's Hospital guideline ([Appendix 4](#)) or, for any particular investigational site, Institutional Review Board (IRB) eligibility guidelines for pediatric blood collection relevant to that site
17. Demonstrate normal values on clinical laboratory coagulation tests (prothrombin time [PT]/international normalized ratio [INR], and activated partial thromboplastin time [PTT]) within 30 days prior to PK Night 1

Subjects who have completed Part 1 of the study are eligible to re-enroll in Part 2 regardless of their current Xyrem treatment status if they meet Inclusion Criteria 4, 5, 11, and 12 and the following criteria at the Part 2 Screening visit (Visit 17) and the first drug-dispensing visit (Visit 18):

18. Are less than 18 years of age
19. If currently being treated with Xyrem, the subject is on a stable dose
20. If currently being treated with Xyrem, the subject's total twice nightly Xyrem dose must be no higher than 9 g/night

### 4.3 Exclusion Criteria

Subjects who demonstrate any of the following will be excluded from Part 1 of the study.

1. Inability to understand assent or follow study instructions for any reason, in the opinion of the Investigator
2. Parent(s) or guardian(s) unable to comply with the requirements of the study for any reason, in the opinion of the Investigator
3. Previously treated with Xyrem and discontinued Xyrem treatment because of lack of efficacy and/or tolerability issues
4. Narcolepsy secondary to another medical condition, e.g., CNS injury or lesion
5. Restless leg syndrome (RLS) requiring treatment other than iron supplements
6. Succinic semi-aldehyde dehydrogenase deficiency (SSADH)
7. Uncontrolled hypothyroidism
8. History of seizure disorders
9. History of head trauma associated with loss of consciousness
10. Evidence of sleep-disordered breathing including:
  - a. Presence of clinically significant obstructive or central sleep apnea as determined by the Investigator or documented previously; or
  - b. Obstructive AHI >5 for subjects 7-11 years of age or obstructive AHI >10 for subjects 12-17 years of age; or
  - c. Oxygen saturation nadir  $\leq$ 85% at night; or

- d. Clinically significant hypoventilation
11. Oxygen saturation level <95% for at least 5 minutes on room air as measured by pulse oximetry while fully awake during daytime monitoring, or subjects with known or suspected respiratory difficulty, or any condition that may compromise a subject's breathing. If oxygen saturation values lower than 95% are observed at study sites at high geographic elevations and are acceptable to the Investigator, enrollment of the subject requires permission from the Medical Monitor
  12. Past or current major thought disorder, e.g., schizophrenia, paranoia, mania, etc.
  13. Recent history of clinically significant parasomnia (e.g., sleep walking, REM behavior disorder, etc.) that would negatively affect the conduct of the study
  14. Current suicidal risk as determined from history or Columbia Suicide Severity Rating Scale (C-SSRS) or history of suicide attempt
  15. Clinically significant depression independent of narcolepsy symptoms
    - o If the T-score is at or above 65 on the Children's Depression Inventory 2nd Edition Self-Report Short Version (CDI 2:SR[S]), an evaluation of depression by the Investigator (if qualified as a mental health professional) or by the Investigator in consultation with a mental health professional must be performed to exclude a clinically significant depression
  16. This criterion was removed during Amendment 2
  17. Other documented clinically significant condition (including unstable medical and/or psychiatric conditions, chronic disease other than narcolepsy with cataplexy, porphyria, or history or presence of another neurological disorder) that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the Investigator
  18. An electrocardiogram (ECG) with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the Investigator
  19. Any clinically significant laboratory abnormality as determined by the Investigator
  20. A positive pregnancy test result at screening (pregnancy tests will be performed for any female subject who has reached menarche)
  21. A positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject)
  22. Treatment with benzodiazepines, non-benzodiazepine anxiolytics/hypnotics/sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, ethosuximide 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 Monitor)
  23. Treatment with any other medications that have anticonvulsant effect (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], or tricyclic antidepressants [TCAs]) within 1 month before Part 1 Screening
  24. Current treatment with oral isotretinoin
  25. Inability to fast for 2 hours before the first dose through 4 hours after the last dose of Xyrem on PSG and PK nights
  26. Lack of parental (or legal guardian) commitment to ensuring home situation is safe for Xyrem use, in the opinion of Investigator

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27. Received any investigational drug within 30 days or 5 half-lives (whichever is longer) before Screening
28. Allergy to any components of topical, local anesthetics that might be used for blood collection (not applicable if numbing agents will not be used)
29. Allergy or sensitivity to malic acid, sucralose, or ingredients in the study drug formulation and/or the flavorant, if used
30. This criterion was removed during Amendment 4

In addition to the above exclusion criteria, prior to participating in the PK evaluation, subjects must not demonstrate any of the following:

31. Hemoglobin less than normal range for age and gender at Screening or at the end of the Double-Blind Period, whichever is closer to PK nights
32. Use of tobacco products or products for smoking cessation within 90 days before PK Night 1, including nicotine-containing products, or history of significant use of tobacco (>10 cigarettes or equivalent per day) within 3 years prior to PK Night 1
33. This criterion was removed during Amendment 2
34. Noncompliance with prescribed Xyrem regimen in the 2 weeks prior to the first PK night

Subjects will be excluded from re-enrolling in Part 2 if they meet Exclusion Criteria 1-10, 12, 17, 19-22, 24, 26-29 or any of the following criteria at the Part 2 Screening visit (Visit 17) and the first drug-dispensing visit (Visit 18):

35. Have not completed Part 1
36. If they are  $\geq 18$  years of age
37. If they have suicidal risk or clinically significant depression independent of narcolepsy symptoms as determined by the Investigator

#### **4.4 Screening Eligibility**

*Note: Title previously read "Screening and Randomization Eligibility". The reference of randomization has been removed due to discontinuation of the placebo treatment in the Double-Blind Treatment Period.*

Subjects will be considered eligible for Part 1 screening if they meet the Part 1 inclusion criteria and do not meet any Part 1 exclusion criteria. Subjects who do not meet eligibility criteria at Part 1 Screening will be considered screen failures; however, subjects may be rescreened for Part 1 if they

- 1) Failed to meet eligibility because of a T-score above 65 on the MASC-10 under Protocol Amendment 1
- 2) Failed to meet eligibility because of being negative on HLA DQB1:0602 under Protocol Amendment 1 or 2
- 3) Failed to meet eligibility because of a T-score at or above 65 on CDI 2:SR[S] under Protocol Amendment 1 or 2 (In this case, permission of the Medical Monitor is required before the subject is rescreened.)

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In addition, rescreening following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary in the unstable state (e.g., unstable hypothyroidism) is permitted only with the permission of the Medical Monitor.

Under Amendment 5, subjects who re-enroll in the study must complete the Part 2 Screening. Subjects who re-enroll within 2 weeks after completing Visit 15 in Part 1 of the study do not require clinical laboratory tests, a urine drug screen, an alcohol test, or a serum pregnancy test at the Part 2 Screening visit. For these subjects, the screening visit (Visit 17) and the first drug-dispensing visit (Visit 18) may occur on the same day.

## 5 STUDY TREATMENT(S)

### 5.1 Description of Treatment

Xyrem<sup>®</sup> (sodium oxybate) oral solution, 500 mg/mL

Xyrem Placebo: a sodium citrate solution prepared in equimolar concentration to sodium in the 500 mg/mL Xyrem (sodium oxybate) oral solution and pH adjusted with malic acid (Placebo treatment only applicable to subjects who had already entered the Double-Blind Treatment prior to Amendment 4 becoming effective).

The bioequivalence of the study drug prepared in a flavored diluent versus prepared in water has been evaluated, and bioequivalence has been established. If available, a flavorant that can be added to the water that is used as diluent will be provided for study drug preparation if flavored diluent is requested by the subject/parent/guardian for palatability. Sucralose in the flavorant is equivalent to 28 mg sucralose in 60 mL, or 56 mg per daily intake of Xyrem prepared with flavored diluent. The FDA acceptable daily intake (ADI) for sucralose is 5 mg/kg body weight/day ([Federal Register, Vol. 63, No. 64, 1998](#)) and the European Union ADI is 0 – 15 mg/kg body weight ([SCF/CS/ADDS/EDUL/190 Final 12/9/2000](#)).

### 5.2 Treatment Administered

Subjects who have been titrated to a stable dose of Xyrem prior to study entry will remain on their stable dose and regimen of Xyrem for 3 weeks during the Stable-Dose Period.

Xyrem-naïve subjects entering Part 1 and subjects re-enrolling in Part 2 who have been off Xyrem for  $\geq 1$  month will be titrated on Xyrem over a period of up to 10 weeks. Xyrem doses are administered in two equally divided doses 2.5 to 4 hours apart. Dose initiation and titration will be based on the subject's weight as described in [Table 1](#). Dose adjustment during the Part 1 and Part 2 titration periods will proceed at a rate of  $\leq 1$  g/night/week for subjects  $< 45$  kg, and  $\leq 1.5$  g/night/week for subjects  $\geq 45$  kg, to a dose level no higher than the maximum dose described in [Table 1](#). Once the Investigator is satisfied that the Xyrem dose has been optimized, the subject may enter the 2-week Stable-Dose Period if in Part 1 of the study or continue the Open-Label Continuation Period if in Part 2.

At the end of the Stable-Dose Period, subjects who had entered the Double-Blind Period prior to Amendment 4 becoming effective were randomized 1:1 to receive either Xyrem or Xyrem placebo during the Double-Blind Treatment Period as follows:

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- Xyrem: Active Xyrem will be continued as a double-blind treatment at the stable dose taken and regimen used in the previous 2 weeks
- Placebo: Xyrem placebo will be initiated as a double-blind treatment at a volume and regimen equivalent to that of the stable dose of Xyrem taken in the previous 2 weeks.

During the Double-Blind Period, subjects will remain on the same dosing regimen they used during the Stable-Dose Period, with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart.

Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment during this period.

During the Part 1 Open-Label Safety Period and following titration in the Part 2 Open-Label Continuation Period subjects may take two equally divided doses or two unequally divided doses with the exception of PK nights, if applicable. Xyrem dose adjustment due to tolerability and efficacy is permitted. Xyrem dose uptitration is allowed at no more than 1.5 g/night. Only doses that match the printed gradations (lines) on the dosing syringe are permitted.

Study Drug will be dispensed at clinic visits and, if applicable, at intervals specified by State or local regulations. Xyrem doses on PSG and PK nights will be administered by or under the supervision of qualified study site personnel. Each Xyrem dose will be diluted with 60 mL of water. On PK nights, Xyrem doses will be followed by 180 mL of water. Subjects will continue to take their usual nightly dose of Xyrem on non-PSG and non-PK nights.

The actual time of dosing for each dose administered on PSG and PK nights will be recorded.

### 5.3 Selection and Timing of Dose for Each Subject

In the studies reported in the literature, Xyrem doses used in children and adolescents were generally lower than the mean dose reported in adults (7.5 g/night). In one of these published studies, children with pre-pubertal onset of narcolepsy took a lower maximal Xyrem dose than those with peri- or post-pubertal onset ([Aran et al. 2010](#)).

Data from the Central Pharmacy that dispenses Xyrem in the US also indicate that most children take lower doses than adults, as would be expected if there were no great differences in metabolism between children and adults and if effective doses were generally based on a mg/kg dose.

Proposed starting doses and titration increments based on weight will be assessed in this study ([Table 1](#)).

Sodium oxybate has a half-life of approximately 0.5 to 1 hour. Pharmacologic doses of sodium oxybate have clinical sedative effects that typically last 2 to 4 hours. Sodium oxybate in divided nightly doses has been studied in patients with narcolepsy and patients with fibromyalgia.

For this study, doses will be taken twice nightly. Each divided dose must match a printed line on the dosing syringe that is provided. Doses may be taken at the following times:

- When the first dose can be taken at bedtime, the first dose should be taken at bedtime while in bed, and the second dose should be taken 2.5 to 4 hours later.

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- When the first dose cannot be taken at bedtime, the first dose should be taken after bedtime while in bed, and the second dose should be taken 2.5 to 4 hours later.

Investigators should caution subjects about operating hazardous machinery, including automobiles or airplanes, or going to school alone until subjects are reasonably certain that study drug does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Subjects should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of study drug.

On PK Night 1, subjects in the PK evaluation will receive one half of their usual (stable) total nightly Xyrem dose (administered as two equally divided doses, given at bedtime and 4 hours later while in bed). On PK Night 2, PK subjects will receive their usual nightly dose (administered as two equally divided doses, given at bedtime and 4 hours later while in bed). Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see [Section 3.1.7](#)). Blood samples for PK assessment collected on these PK nights will allow assessment of dose proportionality within subjects.

#### **5.4 Method of Assigning Subjects to Treatment Groups**

At the beginning of the Double-Blind Treatment Period, subjects who entered this period prior to Amendment 4 becoming effective had been randomized to either Xyrem at the stable dose established in the previous 2 weeks or to Xyrem placebo at a volume equivalent to the Xyrem dose that was established in the previous 2 weeks. During the Double-Blind Period, subjects will remain on the same dosing regimen they used during the Stable-Dose Period, with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart.

Subjects who enter the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment.

#### **5.5 Randomization**

Randomization only applies to subjects who had entered the Double-Blind Randomized-Withdrawal Period prior to Amendment 4 becoming effective.

Prior to Amendment 4, a statistician selected by Jazz Pharmaceuticals specified a dynamic randomization algorithm to assign treatments for the double-blind portion of the trial. The randomization will balance treatment assignment for each age group (7 to 11 years and 12 to 17 years), for prior Xyrem usage (subjects on Xyrem at study entry and Xyrem-naïve subjects), and for location (US and ex-US).

If emergency unblinding is required, for subjects who entered the double-blind period prior to Amendment 4 becoming effective, the double-blind treatment assignment will be provided to the Investigator by an Interactive Voice Recognition System (IVRS) or Interactive Web Response System (IWRS). The treatment assignments for approximately 35 subjects were

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available to the DSMB upon interim analysis. At other times, treatment assignments will be available to the DSMB upon request to address safety concerns. All treatment assignments will be generally available upon final unblinding of the double-blind portion of the study.

## 5.6 Blinding

Blinding only applies to subjects who had entered the Double-Blind Randomized-Withdrawal Period before Amendment 4 becoming effective. A double-blind approach had been used during the Double-Blind Treatment Period for subjects entering this period before Amendment 4 becoming effective. Xyrem and Xyrem placebo oral solution were matched in volume, flavor, and appearance to ensure adequate blinding.

## 5.7 Concomitant Therapy

In this study, the following medications are prohibited:

- Benzodiazepines, non-benzodiazepine anxiolytics/hypnotics/sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, and ethosuximide are prohibited during the study and must have been discontinued within 2 weeks prior to the beginning of the Stable-Dose Period for subjects on Xyrem at study entry and the beginning of the Open-Label Titration Period for Xyrem-naïve subjects. (Discontinuation for the purpose of study enrollment is only permitted if considered safe by the Investigator and approved by the Medical Monitor.) If a subject undergoes short-term out-patient procedures during the study and requires opioids or benzodiazepine use, study drug may be held for one night while these drugs are given. If opioid or benzodiazepine use is required for multiple days, the subject should be discontinued from the study.
- Other antiepileptic therapies (e.g., SNRI, SSRI, or TCA) are prohibited during Part 1 and must have been discontinued within 1 month before Part 1 Screening. (Discontinuation for the purpose of study enrollment is only permitted if considered safe by the Investigator and approved by the Medical Monitor.)
- Oral isotretinoin (Accutane) is prohibited during the study.
- Investigational drugs other than study drug are prohibited during the study.

The following concomitant medications are permitted during the study with the following stipulations:

- Stimulant therapy may be continued, adjusted, or initiated during the study; however, prior to Amendment 4, stimulant use if any must be a stable dose throughout the Stable Dose and Double-Blind periods.
- Other antiepileptic therapies may be allowed in Part 2 of the study
- Vitamins in normal doses may be continued (herbal supplements are prohibited)
- Acetaminophen (paracetamol) for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:
  - Subjects 7 to 11 years of age: no more than 325 mg every 4 to 6 hours, not to exceed 1625 mg in 24 hours

- Subjects 12 years of age and older: no more than 650 mg every 4 to 6 hours, not to exceed 3250 mg in 24 hours
- Ibuprofen for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:
  - Subjects 7 to 11 years of age: no more than 100 mg every 6 to 8 hours, not to exceed 400 mg in 24 hours
  - Subjects 12 years of age and older: no more than 200 mg every 4 to 6 hours, not to exceed 1200 mg in 24 hours
- Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued
- Local topical anesthetic agent for placement of indwelling catheter or before any blood draws
- Non-sedating antihistamines
- Anti-inflammatories for pain
- Chronic topical or oral antibiotics for acne
- Over-the-counter (OTC) decongestants.

All concomitant medications taken during the study will be recorded on the Concomitant Medications case report form (CRF) with indication, total daily dose, and dates of drug administration.

## 5.8 Restrictions

### 5.8.1 Prior Therapy

In addition to Xyrem and stimulant treatment at study entry, subjects may continue prescription and OTC medications with the exception of the prohibited medications listed in [Section 5.7](#). Also, subjects who used any other investigational drug within 30 days or five half-lives (whichever is longer) before Part 1 or Part 2 Screening, or plan to use an investigational drug (other than the study drug) during the study will not be allowed to enter the study.

### 5.8.2 Fluid and Food Intake

#### **For all PSG and PK nights, with the exception of the Screening PSG for Xyrem-naïve subjects:**

During PSG and PK nights, all subjects will be required to eat a light dinner 2 hours before dosing and refrain from caffeinated products. A light dinner may be provided at home or at the study site, but must be eaten at least 2 hours before dosing. The light dinners on each PSG or PK night should be of the same or similar content. The Investigator will verify with the parent or guardian that a light dinner was consumed by the subject. Subjects will take Xyrem (diluted with 60 mL of water or flavored diluent if requested and available); subjects in the PK group will follow the diluted Xyrem with 180 mL of water. Following the light dinner, no food will be allowed until the following morning, approximately 8 hours after the first dose of Xyrem. Water is allowed at night, but may not be taken 1 hour before or after dosing during the PK nights. If the subject prefers to eat breakfast at the study center after the PSG or PK night, a breakfast will be provided.

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### **Screening PSG for subjects who are Xyrem naïve:**

Xyrem-naïve subjects will not have meal restrictions but must refrain from caffeinated products prior to the Screening PSG. Following the subject's dinner, no food will be allowed until the following morning; however, subjects may drink water during the night if desired. If the subject prefers to eat breakfast at the study center after the PSG night, a breakfast will be provided.

#### **5.8.3 Subject Activity Restrictions**

Subjects should take study drug while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy.

On PSG and PK nights, all subjects who receive study drug should remain in bed after the first Xyrem dose for at least 8 hours. If it is necessary for subjects to move about during this time, they must be assisted.

### **5.9 Treatment Compliance**

The number of bottles of clinical study medication dispensed 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. In addition, subjects (if needed, with the help of caregiver) will complete an electronic Study Drug Dosing Diary ([Appendix 12](#)) every morning throughout Part 1 to document that doses of study drug were taken overnight and an electronic Stimulant Dosing Diary ([Appendix 13](#)) every evening through the Double-Blind Treatment Period to document that their regular stimulant dose was taken, if applicable, during the day). Compliance will be assessed throughout the trial based on a subject's prescribed dose, data recorded in the subject's Dosing Diaries (Part 1 only), and volume of solution returned.

On PSG and PK nights, Xyrem will be administered by and taken in the presence of study personnel. Compliance with drug administration will be confirmed by watching the subjects swallowing the solution.

### **5.10 Drug Discrepancies**

Study personnel will note if there is a significant difference in the actual volume and/or amount of study drug returned at each visit compared with the volume and/or amount expected to be returned. If such a difference is found, study personnel will take appropriate action, which may include checking the subject's/parent(s)/guardian(s) dosing technique, re-educating the subject/parent(s)/guardian(s) on proper dosing, and/or addressing potential abuse and/or diversion.

### **5.11 Packaging and Labeling**

Jazz Pharmaceuticals will provide the clinical site with a supply of Xyrem (sodium oxybate) oral solution, 500 mg/mL, for use during all phases of the study. Xyrem placebo (sodium citrate oral solution) was supplied for use during the Double-Blind Treatment Period for subjects entering this period prior to Amendment 4 becoming effective. The flavorant will

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also be provided, if available, to the clinical site. The flavored diluent will consist of a commercially available flavored unsweetened beverage mix sweetened with sucralose and added to water.

All packaging and labeling operations of Xyrem and Xyrem placebo will be performed according to current Good Manufacturing Practices (cGMPs) and Good Clinical Practices (GCPs).

## **5.12 Storage and Accountability**

All study medications will be stored, inventoried, reconciled, and retained or destroyed according to applicable state and federal regulations and instructions from Jazz Pharmaceuticals. Xyrem must be stored according to regulations for a Drug Enforcement Administration (DEA) Schedule III controlled substance in the US and according to any other regional regulations that apply. Jazz Pharmaceuticals will specify the conditions under which drug is stored.

The Investigator or designated pharmacist will maintain accurate records of receipt of all study drugs, including dates of dispensing and receipt. At the study site, study drug supplies must be kept in a secure area and dispensed according to the protocol. Unused (or partially used) supplies must be accounted for on the drug inventory record. Receipt and dispensing of all study drugs must be documented throughout the study and reconciled at study completion. The Investigator must provide a written explanation for any missing study drug. After review of study drug accountability logs at study completion, one copy of the drug inventory record will be retained by the site and the other inventory record will be retained by the sponsor in the Study Master File.

All labels, bottles, and unused Xyrem and Xyrem placebo must be destroyed or returned to Jazz Pharmaceuticals according to written instructions from Jazz Pharmaceuticals or its designee at the completion of the study for reconciliation and destruction. Used bottles of study drug will be destroyed upon Jazz Pharmaceuticals' instruction following the review of study drug accountability. The Investigator must provide a written explanation for any missing study drug.

## **5.13 Investigational Product Retention at Study Site**

Following study completion and notification by the Sponsor, investigational products (Xyrem and Xyrem placebo) do not need to be retained at the study site for FDA testing purposes.

# **6 STUDY PROCEDURES**

## **6.1 Assent and Informed Consent**

All subjects will provide assent and their parent(s) or guardian(s) will give written informed consent in accordance with local IRB/IEC requirements before the performance of any study related procedures.

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Each subject's chart will have the subject's assent documented and the informed consent form (ICF, most current version, if applicable) signed by the parent or guardian for study participation, and for PK evaluation if applicable, attached to it. When the study treatment is completed and the CRF has been monitored, the assent documentation and the ICF will be kept in the Investigator's central study file.

## 6.2 Demographics

Demographics will be collected at Part 1 Screening. The date of the subject's assent and the date the parent or guardian signed the ICF will be collected. The date of the assent/consent for PK evaluation will also be collected; however, it may be after Part 1 Screening as long as the assent/consent is obtained before participation in the PK evaluation. Demographics will include the subject's age (as indicated by date of birth, month and year of birth, year of birth, or age at screening, as required by regional or national regulations), sex, ethnicity, and race.

Contact information of the parent or guardian will be obtained at Part 1 Screening and confirmed on admission to the sleep laboratory on the PSG nights and to the clinic on PK nights. Contact information will be updated at Part 2 Screening. This information will not be collected by the Sponsor.

## 6.3 Medical History

The subject's medical history will be taken at Part 1 Screening to ensure suitability of each subject for enrollment. Past (prior to any narcolepsy treatment) and current symptoms of narcolepsy including cataplexy, EDS, hallucinations, sleep paralysis, and DNS will be recorded. The subject's usual Xyrem regimen, if applicable, including how Xyrem is prepared, usual times taken, and the usual bedtime and awakening time will also be recorded. The Investigator will assess the severity of the subject's cataplexy and narcolepsy overall prior to any treatment by completing a clinical global impression of severity (CGIs) for historical narcolepsy overall and a CGIs for historical cataplexy severity (see [Section 6.6.7](#)). If a subject re-enrolls in Part 2, their previously recorded medical history will be reviewed and updated. In addition, any new medical history that occurs after the last Part 1 study visit (Visit 16) and prior to re-enrollment will be recorded. This would include any new clinically significant condition with onset after Visit 16 until assent/consent in Part 2.

## 6.4 Physical Examination

A full review of body systems should be obtained on each subject. Physical examinations will be conducted at the Part 1 Screening Visit, the end of the Double-Blind Treatment Period, and at Visit 15 (Week 52 or Part 1 early termination) and will include a full examination of body systems (except a breast and genitourinary examination other than the observational evaluation needed for the Tanner Stage Assessment; [Appendix 5](#)), a brief neurological examination, and height and body weight measurements.

An additional brief neurological exam will be performed prior to allowing the subject to be discharged the morning after PSG and PK nights (not applicable for the screening PSG for subjects who are naïve to Xyrem).

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Tanner Stage assessments classifying sexual maturity will be conducted at Part 1 Screening and at Visit 15 (Week 52 or Part 1 early termination).

A physical examination will also be conducted at the Part 2 Screening visit and will include a full examination of body systems (except a breast and genitourinary examination), a brief neurological examination, and height and body weight measurements.

## 6.5 Vital Signs and Pulse Oximetry

Vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) will be monitored and recorded on the CRF after the subject has been resting for at least 5 minutes. Vital signs will be collected at each onsite visit in both Part 1 and Part 2 ([Appendix 1](#), [Appendix 2](#), [Appendix 22](#), [Appendix 23](#), and [Appendix 24](#)).

On PSG nights, vital signs will be measured at the times specified in the schedules of events ([Appendix 1.2](#) [subjects on Xyrem at study entry] and [Appendix 2.3](#) [Xyrem-naïve subjects]). While the subject is being monitored with PSG, the respiratory and heart rate will be captured as part of the PSG parameters. At times when the subject is not undergoing PSG, the respiratory rate will be counted by visual inspection of thoracic movement and will be assessed over 30 seconds, and the pulse/heart rate will be taken.

On PK nights, vital signs will be measured at the times specified in the schedule of events for PK nights ([Appendix 3](#)).

Oxygen saturation by pulse oximetry will be measured while the subject is fully awake on room air and recorded at Part 1 Screening and on the mornings prior to discharge following PSG (excluding screening PSG for Xyrem-naïve subjects) and PK nights.

On PSG nights, for subjects receiving study drug, oxygen saturation (SpO<sub>2</sub>) will be monitored continuously via PSG from the time immediately before the first dose through 8 hours after the first dose and will be recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose ([Appendix 1.2](#) and [Appendix 2.3](#)). During the screening PSG for subjects who are Xyrem naïve, SpO<sub>2</sub> will be monitored as part of the PSG parameters to determine obstructive sleep apnea (OSA) status. End tidal CO<sub>2</sub> (EtCO<sub>2</sub>) or transcutaneous CO<sub>2</sub> (TcCO<sub>2</sub>) will be monitored and recorded at sites where monitoring is routinely performed and performance will not negatively impact study conduct.

On PK nights, SpO<sub>2</sub> will be monitored continuously by pulse oximetry from the time immediately before the first dose through 8 hours after the first dose and will be recorded at the times specified in the Schedule of Events for PK nights ([Appendix 3](#)).

## 6.6 Other Assessments

### 6.6.1 Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD])

The ESS is a self-administered questionnaire with 8 questions. It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. It has been validated in narcolepsy and has demonstrated both a high specificity and sensitivity ([Johns 1991, 2000](#)). In the ESS (CHAD) for children and adolescents ([Appendix 6](#)), the third activity was modified to adapt to a school setting, the fourth activity was shortened from

1 hour to 30 minutes, the fifth activity omitted the phrase “when circumstances permit,” the seventh activity was modified to delete the mention of alcohol, and the eighth activity was replaced by the activity of sitting and eating a meal to avoid the redundancy to the fourth activity.

#### 6.6.2 SF-10 Health Survey for Children

The SF-10™ Health Survey for Children ([Appendix 7](#)) is a parent-completed survey that contains 10 questions adapted from the Child Health Questionnaire (CHQ). The SF-10 provides coverage across a wide range of domains, and is scored to produce physical and psychosocial health summary measures. This survey is intended for children between the ages of 5 and 18, and is available with a standard 4-week recall period.

#### 6.6.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a widely used measure of suicidal ideation and behavior ([Appendix 8](#)). The instrument reliably predicts a potential suicide attempt in those who had previously attempted suicide and is able to determine clinically meaningful points at which a person may be at risk for an impending suicide attempt ([Posner et al. 2011](#)). The C-SSRS is available in versions for children and adolescents and for use in clinical trials. The C-SSRS Children’s Baseline/Screening and the C-SSRS Children’s Since Last Visit versions will be used in this study for subjects under 12 years of age. The Baseline/Screening and Since Last Visit versions will be used for subjects 12 years of age and older ([Posner et al. 2011](#) and personal communication).

#### 6.6.4 Children’s Depression Inventory 2<sup>nd</sup> Edition Self-Report Short Version (CDI 2:SR[S])

The Children’s Depression Inventory (CDI) is a widely used pediatric self-report depressive symptoms assessment in clinical trials ([Myers & Winters 2002](#)). It is a comprehensive assessment of depressive symptoms in youth ages 7 to 17 years. The second edition of the CDI Self-Report (CDI 2:SR) contains 28 items to cover the age-appropriate depressive symptoms which cover affective, cognitive, motivational, neurovegetative, and secondary impairment domains. It covers the criterion symptoms of major depressive disorder and dysthymic disorder as operationalized in the DSM-IV. The CDI 2:SR[S] ([Appendix 9](#)) is the short form of CDI 2:SR. It contains 12 items and takes about half the time of the full-length version to administer (5–10 minutes). The short report form covers primarily affective, cognitive, and neurovegetative aspects of depression. It has been shown that the Total Score of the CDI 2:SR[S] is highly correlated to a Total Score on the selected items of the full-length version ([Kovacs 2011](#)). Due to its brevity, the CDI 2:SR[S] is a suitable screening assessment; however, this scale is not validated in pediatric patients with narcolepsy. Many narcolepsy symptoms overlap with items assessed in the CDI 2:SR[S], e.g., feeling tired, not having fun (in order to control cataplexy attacks); therefore, this scale is used only as a screening assessment for the risk of depression in this study.

#### 6.6.5 Multidimensional Anxiety Scale for Children 10-item (MASC-10)

The MASC-10, a short version of the MASC, is a multidimensional measure with ten items that combine the basic anxiety scales from the long version to produce one score that

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indicates the severity of anxiety problems ([Appendix 10](#)). Satisfactory test-retest reliability was demonstrated for this instrument ([March 1997](#), [March & Sullivan 1999](#)).

#### 6.6.6 Cataplexy Frequency Diary

The subject (if needed, with the help of caregiver) will complete a cataplexy frequency diary ([Appendix 11](#)) daily in the evening during Part 1 to record the daily frequency of the subject's cataplexy attacks ([Appendix 1](#) and [Appendix 2](#)).

#### 6.6.7 Clinical Global Impression of Severity (CGIs) Questionnaires

Clinical Global Impression of Severity (CGIs) is a 7-point Likert rating scale and is a widely used assessment in clinical psychopharmacology trials to assess severity of illness. The responses of this investigator-completed scale range from 1 = normal, no signs of illness, to 7 = among the most extremely ill patients. Using the questionnaires described below, Investigators will rate their impression of the severity of the subject's condition before the subject received any narcolepsy treatment (historical) and the severity of the subject's current condition at specified times during Part 1 of the study.

##### 6.6.7.1 CGIs for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment

At Part 1 Screening (Visit 1), Investigators will rate their impression of the severity of the subject's narcolepsy overall prior to any narcolepsy treatment ([Appendix 15](#)).

##### 6.6.7.2 CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment

At Part 1 Screening (Visit 1), Investigators will rate their impression of the severity of the subject's cataplexy prior to any narcolepsy treatment ([Appendix 16](#)).

##### 6.6.7.3 CGIs for Narcolepsy Overall (current condition)

Investigators will rate their impression of the subject's current severity of narcolepsy overall at the following time points: Part 1 Screening (Visit 1), the start of the Stable-Dose Period (Visit 2 [for subjects on Xyrem at study entry]) or beginning of titration (Visit 1.1 [for Xyrem-naïve subjects]) and the end of the Stable-Dose Period (Visit 3) ([Appendix 17](#)).

##### 6.6.7.4 CGIs for Cataplexy Severity (current condition)

Investigators will rate their impression of the subject's current cataplexy severity at the following time points: Part 1 Screening (Visit 1), the start of the Stable-Dose Period (Visit 2 [for subjects on Xyrem at study entry]) or beginning of Part 1 titration (Visit 1.1 [for Xyrem-naïve subjects]) and the end of the Stable-Dose Period (Visit 3) ([Appendix 18](#)).

#### 6.6.8 Patient Global Impression of Change (PGIc) for Narcolepsy Overall

At the end of the Double-Blind Treatment Period (Visit 4), the subject (if needed, with the help of caregiver) will rate his/her narcolepsy overall since the last visit (Visit 3 [end of Stable-Dose Period]) on a 7-point scale ranging from "very much better" to "very much worse" ([Appendix 19](#)). If the subject discontinues during the Double-Blind Treatment Period, he/she will complete the PGIc at Part 1 early termination.

### 6.6.9 Clinician Global Impression of Change (CGIc) for Narcolepsy Overall and for Cataplexy Severity

At the end of the Double-Blind Treatment Period (Visit 4), Investigators will rate their impression of any change in the severity of the subject's narcolepsy overall ([Appendix 20](#)) and their impression of any change in the severity of the subject's cataplexy ([Appendix 21](#)) since the start of the Double-Blind Treatment Period on a 7-point scale ranging from "very much improved" to "very much worse." If the subject discontinues during the Double-Blind Treatment Period, the Investigator will complete the CGIc for narcolepsy overall and for cataplexy severity at Part 1 early termination.

### 6.6.10 Dosing Diaries

Electronic Dosing Diaries will be used to capture both study drug doses taken and, if applicable, stimulant doses taken during Part 1.

#### 6.6.10.1 Study Drug Dosing Diary

The subject (if needed, with the help of caregiver) will complete the Study Drug Dosing Diary ([Appendix 12](#)) each morning, from the Part 1 Screening Visit (Visit 1) for the subjects on Xyrem at study entry and from the start of the Part 1 Open-Label Titration Period (Visit 1.1) for Xyrem-naïve subjects through the end of Part 1 of the study. The diary is completed to capture if the first and second doses of study drug were taken the night before.

#### 6.6.10.2 Stimulant Dosing Diary

The subject (if needed, with the help of caregiver) will complete the Stimulant Dosing Diary ([Appendix 13](#)) each evening, from the Part 1 Screening Visit (Visit 1) for the subjects on Xyrem at study entry and from the start of the Part 1 Open-Label Titration Period (Visit 1.1) for Xyrem-naïve subjects through the end of the Double-Blind Treatment Period. The diary is completed to capture if the regular dose of stimulants was taken that day, if the subject is taking stimulants.

### 6.6.11 School Attendance Diary

The School Attendance Diary will be completed if the subject has school during the last 2 weeks of the Stable-Dose Period and during the Double-Blind Treatment Period. The subject (if needed, with the help of caregiver) will record daily in the diary if the subject had a scheduled school day and if the subject missed the school day because of narcolepsy ([Appendix 14](#)).

### 6.6.12 Plan of referral

The Investigator should have a plan to refer for appropriate care or to provide appropriate care for subjects requiring emergent medical and/or psychiatric care during the course of study participation.

## 6.7 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded with the subject resting supine for at least 5 minutes at Part 1 Screening (Visit 1), the End of the Double-Blind Treatment Period (Visit 4), and the final Part 1 visit (Visit 15) or Part 1 early termination.

## 6.8 Polysomnography (PSG)

A PSG will be performed on PSG nights according to a standard protocol, which will be provided in a manual to each site, at the times specified in the schedules of events. The manual will include all parameters to be recorded, methods, and a scoring appendix. Oxygen saturation will be monitored according to the study center's standard procedures. Cardiac rhythm strips (over 30 seconds), closest to the specified time points with minimum artifact, will be extracted from the PSG data by the core lab.

Standard PSG parameters will be recorded. The PSG parameters of interest include:

- Apnea Index (AI) and Apnea Hypopnea Index (AHI)
- SpO<sub>2</sub> (mean and nadir)

EtCO<sub>2</sub> or TcCO<sub>2</sub> will be recorded at sites where monitoring is routinely performed, provided it does not negatively impact participation or PSG data integrity. In addition, cardiac rhythm strips (30 seconds) will be obtained at 1 h, 4 h (pre-2nd dose), 5 h, and 8 h after the first Xyrem dose for subjects on Xyrem during the PSG.

**Study Personnel on PSG Nights:** A physician, either the Investigator or a Sub-investigator, must be on call and be readily available during PSG nights. An experienced sleep technologist must be present to monitor the PSG during PSG nights.

**Multiple Sleep Latency Test (MSLT):** If the subject has never been diagnosed with narcolepsy with cataplexy and meets all ICSD-3 Type 1 narcolepsy criteria A and B1 at Part 1 Screening other than the MSLT, an MSLT can be conducted during Part 1 Screening, with the permission of the Medical Monitor, to confirm the diagnosis of narcolepsy with cataplexy.

The ICSD-3 diagnostic criteria for narcolepsy with cataplexy are as follows (Type 1, the International Classification of Sleep Disorders 3rd Revised Diagnostic and Coding Manual [ICSD-3]) ([American Academy of Sleep Medicine 2014](#)):

- **Type 1** (hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy):
  - Criteria A and B must be met:**
    - A. Daily periods of irrepressible need to sleep or daytime lapses into sleep for  $\geq 3$  months.
    - B. The presence of one or both of the following:
      1. Cataplexy *and* a mean sleep latency of  $\leq 8$  minutes and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the

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preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either  $\leq 110$  pg/mL or  $< 1/3$  of mean values obtained in normal subjects with the same standardized assay.

## 6.9 Clinical Laboratory Tests

### 6.9.1 Laboratory Parameters

Blood and urine samples for laboratory tests will be collected at times indicated in the Schedules of Events ([Appendix 1](#), [Appendix 2](#), [Appendix 22](#), [Appendix 23](#), and [Appendix 24](#)).

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following:

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**Table 2 List of Laboratory Tests**

Hematology:	Serum Chemistry:
- Complete blood count (CBC)	- Albumin (ALB)
Urinalysis:	- Alkaline phosphatase (AP)
- Protein	- Alanine aminotransferase (ALT; SGPT)
- Glucose	- Aspartate aminotransferase (AST; SGOT)
- Bilirubin	- Blood urea nitrogen (BUN)
- pH	- Calcium (Ca)
- Nitrite	- Carbon dioxide (CO <sub>2</sub> )
- Ketones	- Chloride (Cl)
- Urobilinogen	- Creatinine
- Occult blood	- Creatine kinase
- Leukocyte esterase	- Gamma-glutamyl transferase (GGT)
Microscopic examination for blood, all types of cells and casts.	- Globulin
Serum and urine human chorionic gonadotropin (hCG) (only for females who have reached menarche)	- Glucose
HLA DQB1:0602 haplotype (at Part 1 Screening only, for subjects with no previous documented results available)	- Lactate dehydrogenase (LDH)
Tests of growth and precocious puberty:	- Phosphorus
- Growth hormone (GH)	- Potassium (K)
- Insulin-like growth factor-1 (IGF-1, low sensitivity)	- Sodium (Na)
- Prolactin	- Total bilirubin
- Luteinizing hormone (LH)	- Direct bilirubin
- Follicle Stimulating Hormone (FSH)	- Total cholesterol
- Testosterone	- Total protein
- Estradiol	- Triglycerides
	- Uric acid
	Coagulation (within 30 days prior to PK Night 1 for PK subjects only):
	- Prothrombin time (PT)/International normalized ratio (INR)
	- Activated partial thromboplastin time (PTT)
	Thyroid Function
	- Thyroid stimulating hormone (TSH) (at Part 1 Screening only)

The clinical laboratory tests will be performed at a central or local laboratory. An authorized back-up laboratory, as indicated on the Form FDA 1572 or equivalent, may be used if necessary as an emergency laboratory. The Investigator will supply Jazz Pharmaceuticals or its designee with the back-up laboratory's current licensure and laboratory reference ranges.

Please note exclusionary clinical laboratory parameters listed in the exclusion criteria. In addition, any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment must be re-evaluated. The

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Investigator will provide an explanation of all clinically significant observations. These findings will be reported as AEs.

#### 6.9.1.1 Pregnancy Test

Pregnancy tests will be performed for female subjects who have reached menarche. At Part 1 Screening (Visit 1), the end of the Double-Blind Treatment Period (Visit 4), and Part 2 Screening, a serum pregnancy test will be performed. A urine pregnancy test will be performed at the start of the Part 1 Open-Label Titration Period for Xyrem-naïve subjects (Visit 1.1), at the start of the Stable-Dose Period for subjects previously on Xyrem (Visit 2), and at the final Part 1 visit (Visit 15) or Part 1 early termination ([Appendix 1](#) and [Appendix 2](#)). During Part 2, a urine pregnancy test will be performed at Visit 18 (for re-enrollers only), at every 6-month visit (Visits 24, 30, and 36), and at Part 2 Study Termination/Part 2 Early Termination (Visit 42) ([Appendix 22](#), [Appendix 23](#), and [Appendix 24](#)).

#### 6.9.1.2 Drug and Alcohol Screen

At Part 1 Screening (Visit 1), the beginning of the Part 1 Open-Label Titration Period for Xyrem-naïve subjects (Visit 1.1), the start of the Stable-Dose Period for subjects previously on Xyrem (Visit 2), the end of the Double-Blind Treatment Period (Visit 4), and during the Open-Label Safety Period at Visits 5, 7, 9, 12, and 15 ([Appendix 1](#) and [Appendix 2](#)), an alcohol test and a panel of urinary drug screens will be performed. During Part 2, an alcohol test and a panel of urinary drug screens will be performed at Part 2 Screening, at Visit 18 (for re-enrollers only), at every 6-month visit (Visits 24, 30, and 36), and at Part 2 Study Termination/Part 2 Early Termination (Visit 42) ([Appendix 22](#), [Appendix 23](#), and [Appendix 24](#)). The panel of urinary drug screens will test for the following prohibited substances. (A positive amphetamine result will not exclude a subject who is taking prescribed amphetamines.)

- Amphetamine (not prescribed)
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine
- Opiates

#### 6.9.1.3 Estimated Total Blood Volume Required by Study

Estimated blood volumes for subjects in Part 1 not participating in the PK evaluation are listed in [Table 3](#). The approximate total blood volume to be collected for study assessments in these subjects is 45.5 mL over a period of one year.

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**Table 3 Estimated Blood Volumes for Assays in Part 1 – Non-PK Subjects**

	Screening (Day -30 to -1) <sup>a</sup>	End of Stable- Dose (Week 3 – Week 10)	End of Double- Blind (Week 5 – Week 12)	Termination (Part 1 Early Termination or Week 52)	Total
Clinical chemistry	7.5 mL	--	7.5 mL	7.5 mL	22.5 mL
TSH		--	--	--	
hCG		--	Included in Chemistry	--	
Girls <8 years old: LH, FSH, estradiol Boys <9 years old: LH, FSH, testosterone		--	--	Included in Chemistry	
Hematology	2 mL	--	2 mL	2 mL	6 mL
HLA DBQ1 602	3 mL	--	--	--	3 mL
GH, prolactin	--	3.5 mL	Included in Chemistry	Included in Chemistry	3.5 mL
IGF-1	--	3.5 mL	3.5 mL	3.5 mL	10.5 mL
Approximate total blood volume per subject	12.5 mL	7 mL	13 mL	13 mL	<b>45.5 mL</b>

<sup>a</sup> If needed, additional screening time may be granted with permission of the Medical Monitor.

Estimated blood volumes for subjects who are participating in the PK evaluation are listed in [Table 4](#). The approximate total blood volume to be collected for study assessments in these subjects is 88.2 mL over a period of one year.

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**Table 4 Estimated Blood Volumes for Assays in Part 1 – PK Subjects**

	Screening (Day -30 to -1) <sup>a</sup>	PK Night 1 <sup>b</sup>	PK Night 2 <sup>b</sup>	End of Stable- Dose (Visit 3)	End of Double- Blind (Visit 4)	Termination (Part 1 Early Termination or Visit 15)	Total
Clinical chemistry	7.5 mL	--	--	--	7.5 mL	7.5 mL	22.5 mL
TSH		--	--	--	--	--	
hCG		--	--	--	Included in Chemistry	--	
Girls <8 years old: LH, FSH, estradiol Boys <9 years old: LH, FSH, testosterone		--	--	--	--	Included in Chemistry	
Hematology	2 mL	--	--	--	2 mL	2 mL	6 mL
HLA DBQ1 602	3 mL	--	--	--	--	--	3 mL
GH, prolactin	--	--	--	3.5 mL	Included in Chemistry	Included in Chemistry	3.5 mL
IGF-1	--	--	--	3.5 mL	3.5 mL	3.5 mL	10.5 mL
Coagulation (Screening)	2.7 mL	--	--	--	--	--	2.7 mL
Pharmacokinetic samples	--	7 × 2 mL	7 × 2 mL	--	--	--	28 mL
Volume for flushing indwelling catheter	--	6 × 1 mL	6 × 1 mL	--	--	--	12 mL
Approximate total blood volume per subject	15.2 mL	20 mL	20 mL	7 mL	13 mL	13 mL	<b>88.2 mL</b>

<sup>a</sup> If needed, additional screening time may be granted with permission of the Medical Monitor.

<sup>b</sup> PK Night 1 and PK Night 2 will occur while subjects are on a stable dose of Xyrem during the study.

For subjects who continue directly into Part 2 from Part 1, no additional blood samples will be collected for clinical laboratory assays. Estimated blood volumes for subjects who re-enroll in Part 2 are listed in Table 5. The approximate total blood volume to be collected for study assessments in these subjects will be 9.5 mL.

**Table 5 Estimated Blood Volumes for Assays in Part 2**

	Part 2 Screening Visit 17 (within 2 weeks before Visit 18) <sup>a</sup>
Clinical chemistry	7.5 mL
hCG	Included in Chemistry
Hematology	2 mL
Approximate total blood volume per subject	9.5 mL

<sup>a</sup> If needed, additional screening time may be granted with permission of the Medical Monitor.

Per the World Health Organization, the existing guidelines for blood sample volume limits (ranging from 1–5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on “minimal risk” to children (Howie 2011). EU Guidelines (2008) for pediatric clinical trials state that, per

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individual, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. Specific guidelines may vary, but a commonly used guidance from Seattle Children's Hospital ([Appendix 4](#)) recommends no more than 2.5% of total blood volume in one blood draw and no more than 5% of the total blood volume in a 30-day period. To ensure that the total blood loss (including PK samples, samples for clinical labs, and any procedural losses) will not exceed the Seattle Children's Hospital's recommendation, EU Guidelines, or any particular investigational site IRB or Independent Ethics Committee (IEC) eligibility guidelines for pediatric blood draws relevant to that site, the following time periods should be maximized for subjects with low body weight participating in the PK evaluation to minimize the amount of blood drawn over 30 days: the Screening Period for subjects on Xyrem at study entry, and the time from Visit 4 to PK Night 1 and from PK Night 2 to Visit 15 for all subjects who participate in PK evaluations during the Open-Label Safety Period.

### 6.9.2 Sample Collection, Storage, and Shipping

A local topical anesthetic agent such as lidocaine/tetracaine (Synera) topical patch, or lidocaine/prilocaine cream (EMLA) may be applied 20-30 minutes or 60-120 minutes, respectively, prior to venipuncture or placement of an indwelling catheter per the site's usual procedures. If a numbing preparation will be used, the study staff will confirm that the subject is not allergic to the preparation prior to the application. Screening blood samples will be obtained by venipuncture. An indwelling catheter for obtaining blood samples for PK assessment will be placed in subjects participating in the PK evaluation on PK nights. If the catheter becomes non-functional (e.g., clogged or infiltrated), a second indwelling catheter may be placed; however, if the attempt to insert this second catheter fails, the PK blood sample collection for that night will be discontinued.

#### 6.9.2.1 Clinical Laboratory Test Samples

The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood and urine sample volumes will meet the laboratory's specifications. The actual time of blood collection for all samples will be recorded.

#### 6.9.2.2 Blood Samples for Pharmacokinetic Analyses

For subjects participating in the PK evaluation, blood samples (2 mL) to measure plasma sodium oxybate concentrations will be collected on two PK nights (PK Night 1 and PK Night 2) at 0 (pre-dose), 0.75, 1.5, 2.5, 4 (pre-2nd dose), 4.75, and 8 hours after the first dose. PK samples will be taken within  $\pm 5$  minutes of the specified time points. The actual time of blood collection for all samples will be recorded.

**Study Personnel on PK Nights:** A physician, either the Investigator or a Sub-investigator, must be on call and be readily available during PK nights. An individual skilled in pediatric venous catheter placement must be present on PK nights when blood samples will be collected and processed for PK evaluation.

To determine sodium oxybate concentrations, blood samples will be drawn according to the time points specified and dispensed into labeled sodium heparin tubes.

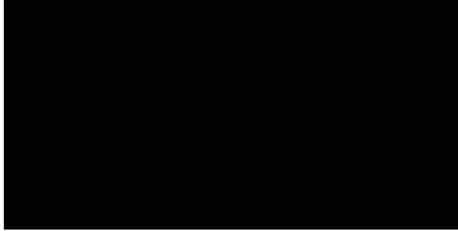
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The blood samples will be collected and processed according to the PK lab manual provided to the sites, and the plasma samples will be shipped to the bioanalytical laboratory on dry ice as directed by the sponsor.

The bioanalysis will be performed by a central bioanalytical laboratory [REDACTED].

Plasma samples for sodium oxybate concentration determination will be shipped Monday through Wednesday via overnight carrier [REDACTED], on the appropriate amount of dry ice, to:



On the day of shipment, please notify [REDACTED] by email [REDACTED] of the pending shipment, including sample shipment tracking information and sample information manifest in Excel format.

## 6.10 Dispensing Study Drug

Subjects on Xyrem at study entry will continue dosing with their own supply of drug during the Part 1 Screening Period; however, appropriate study drug will be provided on the screening PSG night and will be administered by or under the supervision of qualified study site personnel. Study drug will be dispensed to Xyrem-naïve subjects at the beginning of the Part 1 Open-Label Titration Period (Visit 1.1) and to subjects on Xyrem at study entry at the start of the Stable-Dose Period (Visit 2). For subject who re-enroll in Part 2, study drug will be dispensed at Visit 18. Study drug will be dispensed at study visits, excluding phone visits, according to the schedules of events ([Appendix 1](#), [Appendix 2](#), [Appendix 22](#), [Appendix 23](#), and [Appendix 24](#)).

Study drug doses should be prepared with the dosing dispenser (syringe) that is supplied in the study drug kit (dosing instructions provided by Jazz Pharmaceuticals). Instructions for dose administration of the study drug will be provided to subjects/parent(s)/guardian(s) by the site personnel.

Flavorant will be provided if available for study drug preparation if flavored diluent is requested by the subject and deemed appropriate by the Investigator (excluding PSG and PK nights). Instructions for preparation of study drug with flavored diluent will be supplied if flavored diluent is to be used. Additional drug dispensing visits will be made as required by State or local regulations.

On all PSG and PK nights, study drug will be administered by or under the supervision of qualified study site personnel.

The Investigator or designated pharmacist will maintain accurate records for all study drug administered or dispensed.

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## 6.11 Pharmacokinetic Assessments

The PK profile for two doses of Xyrem will be evaluated over an 8-hour period in a subset of subjects on two PK nights. The PK parameters for plasma sodium oxybate concentrations will include, but may not be limited to: the area under the plasma concentration time curve (AUC), maximum plasma drug concentration ( $C_{max}$ ), and time to maximum plasma drug concentration ( $T_{max}$ ), over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours (0.75 hours after the 2nd dose) and 8 hours (4 hours after the 2nd dose) will be measured to estimate peak and residual exposure associated with the second nighttime dose. Dose proportionality will be based on the ratio of AUC values for each subject. Pharmacokinetics will be summarized for the 7-11 and 12-17 year age groups, and a comparison to historical PK data in adults will also be made.

The blood sampling schedule and calculation of required number of patients needed to meet the objectives of this study were determined by Sponsor scientists with expertise in Clinical Pharmacology and Biostatistics.

## 6.12 Adverse Events Assessments

### 6.12.1 Adverse Events (AEs)

All AEs, whether observed by the Investigator, reported by the subject, determined from laboratory findings, or other means, will be recorded on the AE CRF.

- For subjects who participate in Part 1 only, all AEs occurring after assent has been given or the ICF has been signed until the last study visit (through the Study Follow-up Visit or Part 1 early termination) will be recorded.
- For subjects who continue directly into Part 2 from Part 1, all AEs occurring after assent has been given or the ICF has been signed until the last study visit (Part 2 Study Termination Visit/Part 2 Early Termination Visit) will be recorded.
- For subjects who complete Part 1 and re-enroll in Part 2, all AEs occurring after assent has been given or the ICF has been signed in Part 1 until the last Part 1 study visit (through the Safety Follow-up Visit) and all AEs occurring after assent has been given or the ICF has been signed in Part 2 until the last study visit (Part 2 Study Termination Visit/Part 2 Early Termination Visit) will be recorded.

Any new clinically significant condition with onset after the last Part 1 visit (Visit 16) until assent/consent is provided in Part 2 should be recorded as medical history.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug or procedure. During the study, clinically significant adverse changes in clinical status, ECGs, routine laboratory tests, and physical examinations are considered AEs. Any subject complaint associated with such an abnormal finding will also be reported as an AE. Symptoms of narcolepsy are not considered as adverse events unless there is an exacerbation of the symptoms from baseline (Visit 1 for Part 1 and Visit 17 for subjects who re-enroll in Part 2).

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at baseline (Visit 1 for Part 1 and Visit 17 for subjects

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who re-enroll in Part 2); (2) subject deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) abnormal clinically significant laboratory values.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug or procedure, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the AE CRF. Each AE is to be evaluated for duration, intensity, seriousness, and causal relationship to the study drug or procedure. An AE is deemed to be a suspected adverse drug reaction if there is a reasonable possibility that the AE may have been caused by the drug (or medicinal product) or study procedure as defined in Code of Federal Regulations Title 21 CFR 312.32 [a] and ICH E2A II.A.2.

#### 6.12.1.1 Severity

Adverse events will be classified by the Investigator as mild, moderate, or severe as defined below. When the intensity of the AE changes over time, the change in intensity will be recorded on the AE CRF as a new AE.

Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activities is influenced; treatment for symptom(s) may be needed.
Severe	Symptom(s) causes severe discomfort; symptom(s) incapacitate or significantly affect subject's daily life; treatment for symptom(s) may be given and/or subject hospitalized.

#### 6.12.1.2 Relationship to Study Drug or Procedure

The Investigator's assessment of an AE's relationship to study drug or procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the following classification and criteria:

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<p>Related or Suspected to be Related to Study Drug or Procedure</p>	<p>Some temporal relationship exists between the event and the administration of the study drug or procedure and the event is unlikely to be explained by the subject's medical condition, other therapies or accident.</p> <p>The AE follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence:</p> <ul style="list-style-type: none"> <li>• Follows a known or suspected response pattern to the study drug or procedure.</li> <li>• Is confirmed by improvement upon stopping the study drug or procedure or decreasing the dose (dechallenge).</li> <li>• Reappears upon repeated exposure (rechallenge) if medically appropriate.</li> </ul> <p>There is a reasonable possibility that the study drug or procedure caused the event—i.e., there is evidence to suggest a causal relationship. In such case, the AE is considered an <i>adverse reaction</i> (AR). A <i>suspected</i> AR has a lesser degree of certainty about causality than an AR.</p>
<p>Not Related to Study Drug or Procedure</p>	<p>Event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.</p> <p>A reasonable possibility or clinical evidence that the study drug or procedure caused the event is lacking.</p>

### 6.12.1.3 Immediately Reportable Experiences

The following events may occur during participation in this clinical study and must be reported immediately:

- Death or other serious AE (SAE)
- Pregnancy of a subject or subject's partner
- 3-fold or greater elevation above the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) accompanied by an elevation of serum total bilirubin greater than two times the ULN
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN

The events listed above must be reported within 24 hours of first knowledge of the event by study personnel to the appropriate Jazz Pharmaceuticals contact or designee. For immediately reportable experiences, the appropriate form (e.g., SAE Report Form, Pregnancy Form) should be completed as thoroughly as possible and signed by the Investigator or his/her designee before transmittal to Jazz Pharmaceuticals Drug Safety and Pharmacovigilance.

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For SAEs, it is important that the Investigator provide his/her assessment of causality to study drug or procedure at the time of the initial report. If the Investigator's assessment of causality subsequently changes, then a follow-up SAE form must be submitted with a revised causality assessment.

Jazz Pharmaceuticals Drug Safety is required to expedite to global regulatory authorities reports of Serious Adverse Events, including Suspected Unexpected Serious Adverse Reactions (SUSARs), as per the US FDA Code of Federal Regulations, European Commission Clinical Trials Directive (2001/20/EC), and other country-specific regulations.

For the purposes of global expedited adverse event reporting for this clinical trial, the reference safety document for the determination of expectedness is the Investigator's Brochure for Xyrem (sodium oxybate) oral solution for Pediatric Narcolepsy.

#### **SERIOUS ADVERSE EVENTS**

An SAE is an AE that fulfills the following criteria, as per Title 21 CFR 312.32 and ICH E2A.II.B. SAEs must be reported to Jazz Pharmaceuticals or its designee using the SAE Form. The following are defined as SAEs and must be reported within 24 hours of being notified of the event:

- Is fatal (results in death)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one of the outcomes listed above
- Suspected transmission of an infectious agent via a medicinal product *[for EU sites only; EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VI]*

Hospitalization is NOT considered an SAE if:

- It is planned prior to subject entering study
- It is for social reasons and respite care in the absence of any deterioration in the subject's general condition
- It is elective in nature and not related to worsening of an underlying condition
- The subject is treated in the emergency room only AND no 'other' criteria of seriousness apply

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Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, and the occurrence of suicidal ideation.

#### **PREGNANCY**

If a subject [or male subject's partner] becomes pregnant any time after the first dose of study drug until 30 days after the last dose of study drug, the Pregnancy Form should be used to report the pregnancy to Jazz Pharmaceuticals or its designee. Subject pregnancies must be followed until termination of pregnancy or for a minimum of 6 months following the birth of the child. If the pregnancy results in a child birth, the infant must be followed for a minimum of 6 months. The Infant Follow-Up Form should be used to report information regarding the status of the infant.

#### **6.12.1.4 Adverse Event Recording and Reporting**

Each individual AE is to be listed as a separate entry on the AE CRF. The Investigator will provide information about dates of onset and resolution, seriousness, severity, frequency, action(s) taken, outcome, and relationship to study medication.

Documentation of immediately reportable events will follow procedures described in [Section 6.12.1.3](#), Immediately Reportable Experiences.

The Investigator must report to Jazz Pharmaceuticals or its designee all AEs that occur during the study after the informed consent has been signed and assent has been given until the final study visit or early termination, regardless of their relationship to study drug.

If an Investigator becomes aware of an SAE within 30 days after the last dose of study medication, the event must be documented and reported as described in [Section 6.12.1.3](#).

#### **6.12.1.5 Follow-up of Adverse Events and Serious Adverse Events**

Adverse events assessed as not related to study drug or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first. AEs and SAEs assessed as related to study drug or procedure will be followed for as long as necessary to adequately evaluate the subject's safety, or until the event stabilizes, or the subject is lost to follow up. If resolved, a resolution date should be provided, and for SAEs, a follow-up SAE form must be submitted indicating the resolution date. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical.

## 6.13 Concomitant Medication Assessments

Subjects will be asked to refrain from taking the prohibited medications specified in [Section 5.7](#) from the time of Screening until completion of the study. If discontinuation of CNS depressants or any medication poses a safety risk to the subject, the subject should not be enrolled in the study.

All concomitant medications taken during the study will be recorded on the Concomitant Medications CRF with indication, total daily dose, and dates of drug administration.

## 6.14 Removal of Subjects from the Study or Study Drug

All subjects are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The Investigator must withdraw any subject from the study if the subject or subject's parent(s)/guardian(s) requests to stop participating in the study.

The Investigator, Jazz Pharmaceuticals or its designee may remove a subject from the study at any time and for any reason.

If any of the criteria below are met during the study, study drug administration must be stopped and the subject discontinued from the study.

- Suicide risk reported or assessed by C-SSRS
- Clinically significant depression independent of narcolepsy symptoms
  - If the T-score is  $\geq 65$  on CDI 2SR[S], an evaluation of depression by the Investigator (if qualified as a mental health professional) or by the Investigator in consultation with a mental health professional must be performed to exclude clinically significant depression
- Any PSG parameters that indicate, in the judgment of the Investigator, a risk to the subject's safe continued participation
- Subject becomes pregnant
- A positive urine drug screen for benzodiazepines or drugs of abuse (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject) or any suspicion by the investigator of abuse or diversion of study drug
- A positive alcohol test
- 3-fold or greater elevation above the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) accompanied by an elevation of serum total bilirubin greater than two times the ULN
- Liver enzyme (AST, ALT) value greater than or equal to 5 times the ULN
- Experiences an intolerable AE that is related to the study drug and/or procedure
- Develops any clinically significant worsening in narcolepsy symptoms during the Stable-Dose Period
- Develops a clinically significant laboratory or ECG abnormality that is related to the study drug and/or procedure
- Requires a medication that is prohibited by the protocol, with the exception of short-term opioid or benzodiazepine use (see [Section 5.7](#))
- Does not follow guidelines or procedures specified in the protocol

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- 
- Is lost to follow-up
  - Does not continue to meet certain entry criteria or meets certain exclusion criteria during the course of the study
  - Subject reaches his/her 18<sup>th</sup> birthday. Subjects who terminate from Part 2 of the study because they have reached 18 years of age will be considered to have completed the study.

All subjects who prematurely discontinue from the study should have all early termination assessments performed (see Section 6.14.1, Handling of Early Terminations).

The specific reason for the discontinuation should be carefully documented on the termination CRF. If assent or informed consent is withdrawn, the specific reason for withdrawing the assent or informed consent should be stated.

Adverse events resulting in termination will be followed to the satisfactory resolution and determination of outcome as ascertained by the Investigator (and/or Jazz Pharmaceuticals or its designee). The data will be recorded on the appropriate CRF.

#### 6.14.1 Handling of Early Terminations

If a subject terminates early from the study, either at his or her request or the subject's parent(s) or guardian(s), or at the Investigator's discretion, the Investigator will record the reason(s) for early termination on the relevant CRF page and notify the Sponsor immediately. The specific reason for the withdrawal should be carefully documented on the CRF. For instance, rather than stating "withdrew informed consent," the specific reason for withdrawing the informed consent should be stated. All subjects who terminate early from Part 1 should undergo all early termination assessments in [Section 7.4.3](#). All subjects who terminate early from Part 2 should undergo all study termination assessments in [Section 7.5.5](#). Subjects who terminate from Part 2 of the study because they have reached 18 years of age will be considered to have completed the study.

It is vital to obtain follow-up data on any subject who terminated because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

#### 6.15 Sponsor's Termination of Study

Jazz Pharmaceuticals reserves the right to discontinue the study at any time for any reason. Such a termination must be implemented by the Investigator, if instructed to do so by Jazz Pharmaceuticals in a time frame that is compatible with the subject's well-being.

In the situation of a serious issue/event causing study termination, the sudden stop of medication may be warranted. In the event the study is terminated for an administrative reason, Jazz Pharmaceuticals will provide a reasonable period to allow subjects either to be discontinued safely, or to obtain replacement medication. "A reasonable period" is defined as no less than 2 weeks from the time of site notification of impending termination.

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## 6.16 Appropriateness of Measurements

The primary efficacy endpoint (change in weekly number of cataplexy attacks) measure, the Cataplexy Frequency Diary, is similar to the measure used in a prior study to establish efficacy in adults. Cataplexy frequency data will be collected daily in a cataplexy frequency diary. Both the Cataplexy Frequency Diary and the ESS (CHAD) have been evaluated for their face and content validity in children with narcolepsy (Mapi Study JZ13770A). The CGIC has been used extensively in clinical trials.

The PK parameters selected to characterize the PK profile of sodium oxybate are the standardized parameters used to characterize the PK profiles of all drugs. The blood collections for sodium oxybate concentrations will occur at specified time points up to 8 hours after the first Xyrem dose.

The parameters selected to assess the safety of the study drug are appropriate since they are routinely used to assess the safety profile of drugs in clinical studies and pertinent to known risks of Xyrem. The C-SSRS, CDI 2:SR[S], and MASC-10 have been validated for use in the pediatric population.

## 7 STUDY ACTIVITIES

Study activities through the Double-Blind Treatment Period are presented by the following subject groups: subjects on Xyrem at study entry (Section 7.1) and Xyrem-naïve subjects (Section 7.2). PSG night activities are described in Section 7.3. Study activities for the Open-Label Safety Period for all subjects are described in Section 7.4. Study activities for Part 2 (Open-Label Continuation Period) are described in Section 7.5 for subjects continuing directly into Part 2 from Part 1 and in Section 7.6 for subjects re-enrolling in Part 2 after completing Part 1. Additional visits as required by local regulations may be conducted during the study.

The medical monitor may give permission for visits outside any particular visit window to accommodate necessary changes to complete a particular visit (e.g., travel issues, parental or family illness, etc.).

Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment during this period. Subjects entering the Double-Blind Treatment Period before Amendment 4 becoming effective will continue to receive double-blind treatment during this period.

### 7.1 Subjects on Xyrem at Study Entry–Safety, Efficacy, and PK Evaluation

A Schedule of Events for subjects on Xyrem at study entry is in [Appendix 1](#).

#### 7.1.1 Part 1 Screening Visit (Days –30 to -1) Subjects on Xyrem at Study Entry (Visit 1)

After the subject has provided assent and a parent(s) or guardian(s) has signed an ICF in accordance with local IRB/IEC requirements, the subject may be screened for enrollment

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into the study. All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. Screening will occur within 30 days before dosing. (If needed, additional screening time may be granted with permission of the Medical Monitor. However, if it has been more than 45 days since the Screening safety labs pertinent to eligibility were drawn, these labs may need to be repeated as instructed by the Medical Monitor.)

The following study evaluations will be performed:

- Obtain subject assent and ICF signed by parent(s) or guardian(s). If the subject will be participating in the PK evaluation, obtain additional documented assent and consent for the PK evaluation.
- Review the inclusion/exclusion criteria.
- Interview parent(s)/guardian(s) to determine if the home situation is safe for Xyrem use and storage, and assess if there is a risk of use or abuse by family members or others living in the home.
- Obtain demographic information and record contact information for the parent(s) or guardian(s).
- Obtain a medical history, including past (prior to any narcolepsy treatment) and current symptoms of narcolepsy ([Section 6.3](#)).
- Complete the Clinical Global Impression of severity (CGIs) for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment ([Appendix 15](#)) and CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment ([Appendix 16](#)).
- Complete the CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).
- Record usual bedtime and awakening time.
- Record all prior medications, including OTC and health and dietary supplements taken during the 30 days before Screening, and also record any concomitant medications.
- Confirm the subject has been on a stable dose of Xyrem for the previous 2 months. Confirm the subject has been on a stable dose of stimulants, if applicable, for the previous 2 months. Record the subject's prescribed usual dose and regimen of Xyrem and stimulants if applicable.
- Perform a physical examination, including a brief neurological examination and a Tanner Stage Assessment ([Appendix 5](#)) but excluding a full genitourinary exam.
- Record height and weight in ordinary indoor clothes (without shoes).
- Administer the following and record results:
  - ESS (CHAD) ([Appendix 6](#))
  - Columbia-Suicide Severity Rating Scale (C-SSRS) ([Appendix 8](#));  
Baseline/Screening version for subjects  $\geq 12$  years of age and Children's  
Baseline/Screening version for subjects  $< 12$  years of age)

- 
- Children’s Depression Inventory 2nd Edition Self-Report Short Version ([Appendix 9](#))
  - Multi-dimensional Anxiety Scale for Children (MASC-10) ([Appendix 10](#))
  - Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
  - Obtain pulse oximetry reading on room air while the subject is fully awake.
  - Obtain blood samples for the following:
    - Routine hematology, chemistry, and thyroid function (see [Table 2](#))
    - Serum pregnancy test (only for female subjects who have reached menarche)
    - For PK subjects only: coagulation (PT/INR and PTT)
    - HLA DQB1:0602 (if the subject has no previous HLA DQB1:0602 result available and no documented CSF hypocretin level  $\leq 110$  pg/mL)
    - For girls <8 years of age: estradiol, FSH, and LH
    - For boys <9 years of age: testosterone, FSH, and LH
  - Obtain urine samples for urinalysis.
  - Perform alcohol test and urine drug screens.
  - Obtain a 12-lead ECG.
  - Schedule Screening PSG
  - Subjects will continue dosing with their own supply of Xyrem during the Screening Period, with the exception of the Screening PSG Night when Xyrem will be provided.
  - Instruct subjects or parent(s)/guardian(s) on how to complete the Dosing Diaries (Study Drug Dosing Diary in [Appendix 12](#) and Stimulant Dosing Diary in [Appendix 13](#)).
  - The Investigator must thoroughly review results of all screening procedures and confirm all eligibility criteria prior to enrolling the subject in the study. The PSG must be completed and reviewed before the subject is enrolled (For the PSG, follow the procedures in Column 2 of [Table 6](#) for “Subjects on Xyrem at study entry.”)
  - Schedule next visit
- 7.1.2 Start of Stable-Dose Period, Subjects on Xyrem at Study Entry (Visit 2, Day 1)
- Review inclusion/exclusion criteria to determine the subject’s eligibility to continue participating in the study.
  - Record height and weight in ordinary indoor clothes (without shoes).
  - Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
  - Perform alcohol test and urine drug screens.
  - Obtain urine sample for pregnancy test (only for female subjects who have reached menarche).
  - Complete the CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).

- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#); Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Instruct subject and parent(s)/guardian(s) on how to complete the School Attendance Diary ([Appendix 14](#)) if the subject is currently attending school.
- Instruct subjects or parent(s)/guardian(s) on how to complete the Cataplexy Frequency Diary ([Appendix 11](#)).
- Review the dosing diaries for compliance with dosing (Study Drug Dosing Diary in [Appendix 12](#) and Stimulant Dosing Diary in [Appendix 13](#)).
- Record all AEs that occur after assent was given and the ICF was signed on the AE CRF.
- Record all concomitant medications that were taken after assent was given and the ICF was signed on the concomitant medications CRF.
- Dispense study drug at the subject's current stable dose. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Schedule Visit 3 in the morning, and inform subjects/parent(s)/guardian(s) that subjects must be fasting for IGF-1, GH, and prolactin testing when they arrive at the visit.
- For subjects in the PK evaluation during the Stable-Dose Period, perform procedures for PK Night 1 and PK Night 2 in [Section 7.1.3](#).

### 7.1.3 PK Nights 1 and 2 - Subjects Included in the PK Evaluation

Subjects on Xyrem who are willing to participate in the PK evaluation may participate while they are on a stable dose of Xyrem during the study:

- Ensure that coagulations test have been performed within 30 days prior to PK night 1
- Ensure that a light dinner was taken  $> 2$  hours prior to dosing. The light dinner should be the same or similar on both PK Nights. The light meal may be taken at the clinic or at home.
- Confirm parent(s)/guardian(s) contact information.
- Administer study drug:
  - PK Night 1: Administer  $\frac{1}{2}$  of the subject's usual nightly dose, in two equally divided doses 4 hours apart. (Access IVRS/IWRS.)
  - PK Night 2: Administer the subject's usual nightly dose, in two equally divided doses 4 hours apart. (Access IVRS/IWRS.)

Note: Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see [Section 3.1.7](#)).

- Obtain blood samples for sodium oxybate concentrations at the times specified in the schedule of PK Night procedures ([Appendix 3](#)).
- Obtain vital signs at the times specified in the schedule of PK Night procedures ([Appendix 3](#)).
- Monitor SpO<sub>2</sub> continuously by pulse oximetry from immediately before the first dose through 8 hours after the first dose, and record at the times specified in the schedule of PK Night procedures ([Appendix 3](#)). Take an additional measurement while the subject is awake and before release from the clinic.
- Perform a brief neurological exam before discharge on the morning after PK assessment.
- Provide breakfast if the subject prefers to eat at the clinic.
- Ensure that subjects of driving age who received study drug during the PK nights will not be driving themselves when leaving the clinic.

#### 7.1.4 End of Stable-Dose Period/Beginning of the Double-Blind Treatment Period\*, Subjects on Xyrem at Study Entry (Visit 3, Week 3 ±3 days)

\*Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will complete this visit and receive open-label Xyrem during this period.

- Collect a fasting blood sample for GH, IGF-1, and prolactin.
- Provide breakfast for the subject after the fasting blood sample is collected.
- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary.
- Review the Dosing Diaries for compliance with dosing.
- Complete CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#); Since Last Visit version for subjects ≥12 years of age and Children's Since Last Visit version for subjects <12 years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Collect information on school attendance ([Appendix 14](#)) if the subject is currently attending school and will be attending school during the Double-Blind Treatment Period.

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- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Collect study drug dispensed at Visit 2 and assess compliance.
- Schedule next visit (Visit 4) in the morning, and inform subjects/parent(s)/guardian(s) that subjects must be fasting for IGF-1, GH, and prolactin testing when they arrive at the visit.

#### 7.1.5 End Double-Blind Treatment Period, Subjects on Xyrem at Study Entry (Visit 4, Week 5 +3 days)

- Obtain blood samples for the following:
  - Fasting blood sample for GH, IGF-1, and prolactin
  - Routine hematology and chemistry
  - Serum pregnancy test (only for female subjects who have reached menarche)
- Provide breakfast for the subject after the fasting blood sample is collected.
- Perform a physical examination and record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Obtain urine sample for urinalysis.
- Perform alcohol test and urine drug screens for subjects who are continuing into the Open-Label Safety Period.
- Obtain a 12-lead ECG.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Collect information from the School Attendance Diary ([Appendix 14](#)).
- Have the subject complete the PGIC ([Appendix 19](#)). Instruct the subject to rate his/her impression of change since Visit 3 (the end of the Stable-Dose Period).
- Complete CGIc for narcolepsy overall ([Appendix 20](#)) and for cataplexy severity ([Appendix 21](#)).
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#); Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.

- Record all concomitant medications on the concomitant medications CRF.
- Dispense study drug for the Open-Label Safety Period. (Access IVRS/IWRS.)
  - Subjects may take two equally divided doses or two unequally divided doses with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart. Only doses that match the printed gradations (lines) on the dosing syringe are permitted.
  - **For subjects who had entered the Double-Blind Period prior to Amendment 4 becoming effective:**  
Upon entering the Open-Label Safety Period, all subjects will be started at a dose no higher than half the Xyrem dose they received at the end of the Stable-Dose Period or the initiation dose defined in [Table 1](#), whichever is higher. Subjects will then be titrated up to their optimal dose as tolerated according to the Investigator's judgment (the maximum dose should not exceed the doses defined in [Table 1](#) or the stable dose prior to study entry, whichever is higher, and should not be greater than 9 g/night). Xyrem dose uptitration is allowed at no more than 1.5 g/night.
  - **For subjects entering the Double-Blind Period after Amendment 4 becoming effective:**  
Subjects will continue on in the Open-Label Safety Period at their appropriate dose.
- Collect study drug dispensed at Visit 3 and assess compliance.
- Schedule next visit.

#### 7.1.6 Open-Label Safety Evaluation, Subjects on Xyrem at Study Entry (Visit 5, 4 weeks after end of Double-Blind Period)

- Follow procedures in [Section 7.4](#)

## 7.2 Xyrem-naïve Subjects at Study Entry–Safety, Efficacy, and PK Evaluation

A Schedule of Events for subjects who are Xyrem naïve at study entry is in [Appendix 2](#).

### 7.2.1 Part 1 Screening Visit (Days –30 to –1), Xyrem-naïve Subjects (Visit 1)

After the subject has provided assent and a parent(s) or guardian(s) has signed an ICF in accordance with local IRB/IEC requirements, the subject may be screened for enrollment into the study. All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. Screening will occur within 30 days before dosing. (If needed, additional screening time may be granted with permission of the Medical Monitor. However, if it has been more than 45 days since the Screening safety labs pertinent to eligibility were drawn, these labs may need to be repeated as instructed by the Medical Monitor.)

The following study evaluations will be performed:

- 
- Obtain subject assent and ICF signed by parent(s) or guardian(s). If the subject will be participating in the PK evaluation, obtain additional documented assent and consent for the PK evaluation.
  - Review the inclusion/exclusion criteria.
  - Interview parent(s)/guardian(s) to determine if the home situation is safe for Xyrem use and storage, and assess if there is a risk of use or abuse by family members or others living in the home.
  - Obtain demographic information and record contact information for the parent(s) or guardian(s).
  - Obtain a medical history, including past (prior to any narcolepsy treatment) and current symptoms of narcolepsy ([Section 6.3](#)).
  - Complete the CGIs for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment ([Appendix 15](#)) and the CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment ([Appendix 16](#)).
  - Complete CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).
  - Record usual bedtime and awakening time.
  - Record all prior medications, including OTC and health and dietary supplements taken during the 30 days before Screening, and also record any concomitant medications.
  - Perform a physical examination, including a brief neurological examination and a Tanner Stage Assessment ([Appendix 5](#)) but excluding a full genitourinary exam.
  - Record height and weight in ordinary indoor clothes (without shoes).
  - Administer the following and record results:
    - ESS (CHAD) ([Appendix 6](#))
    - C-SSRS ([Appendix 8](#)) – (Baseline/Screening version for subjects  $\geq 12$  years of age and Children's Baseline/Screening version for subjects  $< 12$  years of age)
    - CDI 2:SR[S] ([Appendix 9](#))
    - MASC-10 ([Appendix 10](#))
  - Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
  - Obtain pulse oximetry reading on room air while the subject is fully awake.
  - Obtain blood samples for the following:
    - Routine hematology, chemistry, and thyroid function (see [Table 2](#))
    - Serum pregnancy test (only for female subjects who have reached menarche)
    - HLA DQB1:0602 (if the subject has no previous HLA DQB1:0602 result available and no documented CSF hypocretin level  $\leq 110$  pg/mL)
    - For girls  $< 8$  years of age: estradiol, FSH, and LH
    - For boys  $< 9$  years of age: testosterone, FSH, and LH
  - Obtain urine samples for urinalysis.
  - Perform alcohol test and urine drug screens.

- Obtain a 12-lead ECG.
- Schedule Screening PSG.
- The Investigator must thoroughly review results of all screening procedures and confirm all eligibility criteria prior to enrolling the subject in the study. The PSG must be completed and reviewed before the subject is enrolled (For the PSG, follow the procedures in Column 1 of [Table 6](#) for Xyrem-naïve subjects.)
- Schedule next visit (Visit 1.1) to begin the Open-Label Titration Period.

### 7.2.2 Part 1 Open-Label Titration Period, Xyrem-naïve Subjects

Subjects who are naïve to Xyrem at study entry will be titrated to Xyrem as described in [Section 3.1.2](#). The Open-Label Titration Period may last up to 10 weeks; however, once it is determined that the subject has achieved a maximum clinical benefit in cataplexy and EDS while maintaining tolerability, the subject may be advanced to the Stable-Dose Period. If it is determined that the subject is on a stable dose at a clinic visit (i.e., Visits 1.2, 1.5, or 1.7), the Investigator should perform the Visit 2 procedures to begin the Stable-Dose Period. If it is determined that the subject is on a stable dose at a phone visit (i.e., Visits 1.3, 1.4, or 1.6), the Investigator should schedule Visit 2 as soon as possible to start the Stable-Dose Period. A Schedule of Events for Xyrem-naïve subjects is in [Appendix 2](#).

#### 7.2.2.1 Visit 1.1 Begin Titration (Day 1)

- Review inclusion/exclusion criteria to determine the subject's eligibility to continue participating in the study.
- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Perform alcohol test and urine drug screens.
- Obtain urine sample for pregnancy test (only for female subjects who have reached menarche).
- Complete CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Instruct subjects or parent(s)/guardian(s) on how to complete the Cataplexy Frequency Diary ([Appendix 11](#)) and the Dosing Diaries (Study Drug Dosing Diary in [Appendix 12](#) and Stimulant Dosing Diary in [Appendix 13](#)).
- Record all AEs that occur after assent was given and the ICF was signed on the AE CRF.

- Record all concomitant medications that were taken after assent was given and the ICF was signed on the concomitant medications CRF.
- Determine initial dose, and instruct subject and parent(s)/guardian(s) or parent(s)/guardian(s) on Xyrem dosing.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Schedule next visit.

#### 7.2.2.2 Visit 1.2 (Week 1 +3 days)

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Collect study drug dispensed at Visit 1.1 and assess compliance.
- Schedule next visit.

#### 7.2.2.3 Phone Call Visit 1.3 (Week 2 +3 days)

- Review Cataplexy Frequency Diary, and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.

- Schedule next visit.

#### 7.2.2.4 Phone Call Visit 1.4 (Week 3 +3 days)

- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.
- Schedule next visit.

#### 7.2.2.5 Visit 1.5 (Week 4 $\pm 7$ days)

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Collect study drug dispensed at Visit 1.2 and assess compliance.
- Schedule next visit.

#### 7.2.2.6 Phone Call Visit 1.6 (Week 6 +3 days)

- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:

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- C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
- CDI 2:SR[S] ([Appendix 9](#))
- MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.
- Schedule next visit.

#### 7.2.2.7 Visit 1.7 (Week 8 $\pm$ 7 days)

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Assess subject and determine if additional dose titration is necessary.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Collect study drug dispensed at Visit 1.5 and assess compliance.
- Schedule next visit.

#### 7.2.3 End Titration/Start of Stable-Dose Period, Xyrem-naïve Subjects at Study Entry (Visit 2, Week 10 $\pm$ 3 days)

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))

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- MASC-10 ([Appendix 10](#))
- Instruct subjects or parent(s)/guardian(s) on how to complete the School Attendance Diary ([Appendix 14](#)) if the subject is currently attending school.
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Confirm that a stable dose has been reached (i.e., a dose that achieves a maximum clinical benefit in cataplexy and EDS while maintaining tolerability).
- Collect study drug dispensed at previous onsite visit and assess compliance.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- If the subject has been unable to be titrated to a stable dose of Xyrem in the last 10 weeks, conduct the termination visit and schedule the safety follow-up visit (see procedures in [Section 7.4.3](#) and [7.4.4](#)).
- Schedule the next visit in 14 (+3) days to begin the Double-Blind Treatment Period.

#### 7.2.4 End of Stable-Dose Period/Beginning of the Double-Blind Treatment Period\*, Xyrem-naïve Subjects (Visit 3, Week 12 +3 days)

\*Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will complete this visit and receive open-label Xyrem during this period.

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Review Cataplexy Frequency Diary.
- Review the Dosing Diaries for compliance with dosing.
- Complete CGIs for narcolepsy overall (current condition) ([Appendix 17](#)) and for cataplexy severity (current condition) ([Appendix 18](#)).
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Collect information on school attendance ([Appendix 14](#)) if the subject is currently attending school and will be attending school during the Double-Blind Treatment Period.
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Collect study drug dispensed at Visit 2 and assess compliance.

- Perform an End of Stable-Dose/Pre-Randomization PSG according to procedures in Column 3 of [Table 6](#). (Note: For administrative reasons the terminology for this PSG will retain the reference to “Pre-Randomization”).
- Dispense study drug in the morning after the End of Stable-Dose/Pre-Randomization PSG. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Schedule next visit in the morning, and inform subjects/parent(s)/guardian(s) that subjects must be fasting when they arrive at the visit.

#### 7.2.5 End Double-Blind Treatment Period, Xyrem-naïve Subjects (Visit 4, Week 14 +3 days)

- Obtain blood samples for the following:
  - Fasting blood sample for GH, IGF-1, and prolactin
  - Routine hematology and chemistry (see [Table 2](#))
  - Serum pregnancy test (only for female subjects who have reached menarche)
- Provide breakfast for the subject after the fasting blood sample is collected.
- Perform a physical examination and record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Obtain urine samples for urinalysis.
- Perform alcohol test and urine drug screens for subjects who are continuing into the Open-Label Safety Period.
- Obtain a 12-lead ECG.
- Review Cataplexy Frequency Diary and review the Dosing Diaries for compliance with dosing.
- Collect information from the School Attendance Diary ([Appendix 14](#)).
- Have the subject complete the PGIC ([Appendix 19](#)). Instruct the subject to rate his/her impression of change since Visit 3 (the end of the Stable-Dose Period).
- Complete CGIc for narcolepsy overall ([Appendix 20](#)) and for cataplexy severity ([Appendix 21](#)).
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children’s Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.

- Collect study drug dispensed at Visit 3 and assess compliance.
- Dispense study drug for the Open-Label Safety Period. (Access IVRS/IWRS.)
  - Subjects may take two equally divided doses or two unequally divided doses, with the exception of PK nights (if applicable) when all subjects have to take two equally divided doses 4 hours apart. Only doses that match the printed gradations (lines) on the dosing syringe are permitted.
  - **For subjects who had entered the Double-Blind Treatment Period prior to Amendment 4 becoming effective:**
  - Upon entering the Open-Label Safety Period, all subjects will be started at a dose no higher than half the Xyrem dose they received at the end of the Stable-Dose Period or the initiation dose defined in [Table 1](#), whichever is higher. Subjects will then be titrated up to their optimal dose as tolerated according to the Investigator's judgment (the maximum dose should not exceed the doses defined in [Table 1](#) or the stable dose prior to study entry, whichever is higher, and should not be greater than 9 g/night). Xyrem dose uptitration is allowed at no more than 1.5 g/night.
  - **For subjects entering the Double-Blind Period after Amendment 4 becoming effective:**  
Subjects will continue on in the Open-Label Safety Period at the same dose that they have been taking.
- Schedule next visit.

#### 7.2.6 PK Nights 1 and 2, Xyrem-naïve Subjects

Refer to [Section 7.1.3](#)

#### 7.2.7 Open-Label Safety Evaluation, Xyrem-naïve Subjects

- See procedures in [Section 7.4](#)

### 7.3 PSG Night Procedures for All Subjects

[Table 6](#) lists the procedures for the PSG nights by study period (Screening and End of Stable-Dose/Pre-Randomization\*) and subject population (subjects on Xyrem at study entry and Xyrem-naïve subjects). Note: \*For administrative reasons the terminology for this PSG will retain the reference to "Pre-Randomization".

For all PSG nights when subjects receive study drug, a light dinner should be taken >2 hours prior dosing. The meal should be the same or similar on all PSG nights where dosing with study drug is required. The Investigator will confirm that the light dinner planned and consumed was acceptable. The meal may be taken at the Sleep Lab or at home. No dinner restriction is required for Xyrem-naïve subjects prior to the screening PSG night.

The site will be supplied with appropriate study drug for use on Screening PSG nights. Subjects will bring the study drug dispensed to them for the End of Stable-Dose/Pre-Randomization (Xyrem-naïve subjects only) and End of Study (Part 1) PSGs.

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On PSG nights, when subjects have taken study drug, subjects should be allowed to sleep after the second dose until they wake.

Ensure that subjects of driving age who received study drug during the PSG nights will not be driving themselves when leaving the sleep lab.

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**Table 6 PSG Night Procedures**

1	2	3	4
Screening PSG		End of Stable-Dose/Pre-Randomization PSG*	End of Study (Part 1) PSG or Part 1 Early Termination <sup>a</sup>
Xyrem-naïve subjects	Subjects on Xyrem at study entry	Xyrem-naïve subjects	All subjects
Review inclusion/exclusion	Review inclusion/exclusion	No inclusion/exclusion review needed	No inclusion/exclusion review needed
No dinner restrictions	Light dinner >2 hours before dosing	Light dinner >2 h before dosing	Light dinner >2 h before dosing
Confirm parent/guardian contact information	Confirm parent/guardian contact information	Confirm parent/guardian contact information	Confirm parent/guardian contact information
No dosing	Usual nightly dose of Xyrem divided into 2 doses, 4 h apart	Nightly dose of Stable-dose Xyrem divided into 2 doses, 4 h apart	Nightly Xyrem dose taken at end of Safety Period divided into 2 doses, 4 h apart
Perform PSG	Perform PSG	Perform PSG	Perform PSG
EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>b</sup>	EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>b</sup>	EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>b</sup>	EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>b</sup>
Obtain vital signs <sup>c</sup>	Obtain vital signs <sup>d</sup>	Obtain vital signs <sup>d</sup>	Obtain vital signs <sup>d</sup>
Monitor SpO <sub>2</sub> <sup>e</sup>	Monitor and record SpO <sub>2</sub> <sup>f</sup>	Monitor and record SpO <sub>2</sub> <sup>f</sup>	Monitor and record SpO <sub>2</sub> <sup>f</sup>
Record AEs/Con Meds	Record AEs/Con Meds	Record AEs/Con Meds	Record AEs/Con Meds
---	Brief neuro exam <sup>g</sup>	Brief neuro exam <sup>g</sup>	Brief neuro exam <sup>g</sup>
No blood sample	No blood sample	The morning following the PSG, obtain <b>fasting</b> blood sample for GH, IGF-1, and prolactin	The morning following the PSG, obtain blood samples for <ul style="list-style-type: none"> <li>◦ <b>Fasting</b> blood sample for GH, IGF-1, and prolactin</li> <li>◦ Routine hematology and chemistry</li> <li>◦ For girls &lt;8 years of age: estradiol, FSH, and LH</li> <li>◦ For boys &lt;9 years of age: testosterone, FSH, and LH</li> </ul>
Provide breakfast (if subject prefers to eat at the study center) in the morning after all PSG nights			

GH=growth hormone, IGF-1=insulin-like growth factor-1 (low sensitivity)

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\*For administrative reasons the terminology for this PSG will retain the reference to “Pre-Randomization”.

- a) If the subject withdraws early from Part 1 of the study during the Open-Label Safety Period, perform a PSG if the subject is willing to be dosed with study drug for this PSG night. Part 1 Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
- b) At sites where EtCO<sub>2</sub> or TcCO<sub>2</sub> monitoring is routinely performed.
- c) Obtain vital signs after subject has been resting for at least 5 minutes before start of PSG and prior to release from study center.
- d) Obtain vital signs after subject has been resting for at least 5 minutes at pre-dose and prior to release from study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, heart and respiratory rates are recorded via PSG monitoring.
- e) Monitor SpO<sub>2</sub> to determine obstructive sleep apnea status.
- f) Monitor SpO<sub>2</sub> continuously from immediately before first dose through 8 hours after first dose, and record SpO<sub>2</sub> pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after first dose and before release from study center while subject is awake.
- g) Brief neurological exam before discharge on the morning after the PSG.

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## 7.4 Open-Label Safety Period for All Subjects

A Schedule of Events for subjects in the Open-Label Safety Period is in [Appendix 1.1](#) for subjects on Xyrem at study entry and in [Appendix 2.2](#) for subjects who are Xyrem-naïve at study entry.

### 7.4.1 Visit 5 (4 weeks after end of the Double-Blind Treatment Period) and Visits 7, 9, 12 (Weeks 18, 26, 39 from Day 1)

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Perform urine drug and alcohol test screens.
- Review Cataplexy Frequency Diary.
- Review Study Drug Dosing Diary.
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#); Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Collect study drug dispensed at the previous visit and measure compliance.
- Dispense study drug. (Access IVRS/IWRS.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Schedule the next clinic or phone visit

### PK Evaluation

Once the subject is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit.

- If not done at a previous visit:
  - Obtain additional documented assent and consent for the PK evaluation.
  - Review the inclusion/exclusion criteria for subjects participating in the PK evaluation.
  - Obtain blood samples for coagulation (PT/INR and PTT) within 30 days of PK Night 1
- Follow procedures for PK Nights 1 and 2 in [Section 7.1.3](#).

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#### 7.4.2 Phone Call Visits 6, 8, 10, 11, 13, 14 (Weeks 16, 22, 30, 34, 43, and 48 from Day 1)

- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))

#### 7.4.3 Visit 15 Week 52 or Part 1 Early Termination

If the subject will be continuing directly into Part 2, the Open-Label Continuation Period, see [Section 7.5](#).

- Perform a physical examination, including a brief neurological examination and a Tanner Stage Assessment ([Appendix 5](#)) but excluding a full genitourinary exam.
- Record height and weight in ordinary indoor clothes (without shoes).
- Review Cataplexy Frequency Diary.
- Review Study Drug Dosing Diary.
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))
  - SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting supine for at least 5 minutes.
- Obtain urine samples for urinalysis.
- Perform alcohol test and urine drug screens.
- Obtain urine sample for pregnancy test (only perform for female subjects who have reached menarche).
- Obtain a 12-lead ECG.
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Collect study drug dispensed at the previous visit and measure compliance.
- Perform End of Study (Part 1) PSG according to the procedures for all subjects in Column 4 of [Table 6](#). If the subject withdraws early from the study during the Open-Label Safety Period, perform the PSG if subject is willing to be dosed with study drug

on this PSG night. Part 1 early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.

- Obtain blood samples for the following the morning after the PSG night:
  - Fasting blood sample for GH, IGF-1, and prolactin
  - Routine hematology and chemistry
  - For girls <8 years of age: estradiol, FSH, and LH
  - For boys <9 years of age: testosterone, FSH, and LH
- If the subject will not be continuing into Part 2, record the reason why and schedule the Safety Follow-up visit.

#### 7.4.4 Visit 16 Safety Follow-up Visit

The Safety Follow-up Visit must be completed 14 days (+3 days) after the last dose of study drug for subjects who complete Part 1 of the study and are not continuing directly into Part 2 or for subjects who terminate early from Part 1.

- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting supine for at least 5 minutes.
- Administer the following:
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects <12 years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
- Record all AEs on the AE CRF.

Subjects will not be given study drug during this 2-week follow-up period but are expected to be treated for their cataplexy and EDS with commercially available medications as appropriate during this time by their treating physicians.

### 7.5 Part 2 Open-Label Continuation Period for Subjects Continuing Directly into Part 2 after Completing Part 1

#### 7.5.1 Visit 15 for Subjects Continuing in Part 2 (Onsite)

- Confirm that subject provided assent and ICF signed by parent(s) or guardian(s) for Protocol Amendment 5.
- Perform a physical examination, including a brief neurological examination and a Tanner Stage Assessment ([Appendix 5](#)) but excluding a full genitourinary exam.
- Record height and weight in ordinary indoor clothes (without shoes).
- Review Cataplexy Frequency Diary.
- Review Study Drug Dosing Diary.
- Administer the following:
  - ESS (CHAD) ([Appendix 6](#))

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- SF-10 ([Appendix 7](#))
  - C-SSRS ([Appendix 8](#)) (Since Last Visit version for subjects  $\geq 12$  years of age and Children's Since Last Visit version for subjects  $< 12$  years of age)
  - CDI 2:SR[S] ([Appendix 9](#))
  - MASC-10 ([Appendix 10](#))
  - Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting supine for at least 5 minutes.
  - Obtain urine samples for urinalysis.
  - Perform alcohol test and urine drug screens.
  - Obtain urine sample for pregnancy test (only perform for female subjects who have reached menarche).
  - Obtain a 12-lead ECG.
  - Record all AEs on the AE CRF.
  - Record all concomitant medications on the concomitant medications CRF.
  - Collect study drug dispensed at the previous visit and measure compliance.
  - Perform End of Study (Part 1) PSG according to the procedures for all subjects in Column 4 of [Table 6](#).
  - Obtain blood samples for the following the morning after the PSG night:
    - Fasting blood sample for GH, IGF-1, and prolactin
    - Routine hematology and chemistry
    - For girls  $< 8$  years of age: estradiol, FSH, and LH
    - For boys  $< 9$  years of age: testosterone, FSH, and LH
  - Dispense study drug. (Access Interactive Response Technology [IRT].) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
  - Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur **prior to** the subject's 18<sup>th</sup> birthday.

#### 7.5.2 Visits 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, and 41 (Phone Call)

- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur **prior to** the subject's 18<sup>th</sup> birthday.

#### 7.5.3 Visits 21, 27, 33, and 39 (Onsite)

- Record height and weight in ordinary indoor clothes (without shoes).

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- 
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
  - Record all AEs on the AE CRF.
  - Record all concomitant medications on the concomitant medications CRF.
  - Collect study drug dispensed at the previous visit and measure compliance.
  - Dispense study drug. (Access IRT.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
  - Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur *prior to* the subject's 18<sup>th</sup> birthday.

#### 7.5.4 Visits 24, 30, and 36 (Onsite)

- Record height and weight in ordinary indoor clothes (without shoes).
- Perform alcohol test and urine drug screens.
- Obtain urine sample for pregnancy test (only perform for female subjects who have reached menarche).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Collect study drug dispensed at the previous visit and measure compliance.
- Dispense study drug. (Access IRT.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur *prior to* the subject's 18<sup>th</sup> birthday.

#### 7.5.5 Part 2 Study Termination/Part 2 Early Termination Visit 42 (Onsite)

- Record height and weight in ordinary indoor clothes (without shoes).
- Perform alcohol test and urine drug screens.
- Obtain urine sample for pregnancy test (only perform for female subjects who have reached menarche).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Record all AEs on the AE CRF.
- Record all concomitant medications on the concomitant medications CRF.
- Collect study drug dispensed at the previous visit and measure compliance.

## 7.6 Part 2 Open-Label Continuation Period for Subjects Re-enrolling after Completing Part 1

After the subject has provided assent and a parent(s) or guardian(s) has signed an ICF in accordance with local IRB/IEC requirements, the subject may be screened for re-enrollment in Part 2. All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Part 2 Screening Visit (Visit 17) starts when a subject is registered for Part 2 in IRT. Screening will occur within 2 weeks before dosing. If needed, additional screening time may be granted with permission of the Medical Monitor.

### 7.6.1 Part 2 Screening Visit 17 (Onsite) for Subjects Re-enrolling after Completing Part 1 of the Study

- Obtain subject assent and ICF signed by parent(s) or guardian(s).
- Update the parent or guardian's contact information
- Review the inclusion/exclusion criteria for Part 2.
- Interview parent(s)/guardian(s) to determine if the home situation is safe for Xyrem use and storage, and assess if there is a risk of use or abuse by family members or others living in the home.
- Review the subject's previously recorded medical history and update any new medical history information. Record any new medical history that occurs after Visit 16 and prior to re-enrollment. (Any new clinically significant condition with onset after the last Part 1 visit (Visit 16) until assent/consent is provided in Part 2 should be recorded as medical history.)
- Record all prior medications, including OTC and health and dietary supplements taken during the 2 weeks before Screening. Also record any concomitant medications.
- Confirm the subject's current Xyrem usage. If the subject is currently on Xyrem, record the subject's prescribed usual dose and regimen of Xyrem. If currently on Xyrem, the subject should be on a stable dose. If the subject has been off Xyrem, record if the subject has been off Xyrem for  $\geq 1$  month.
- Perform a physical examination, including a brief neurological examination.
- Record height and weight in ordinary indoor clothes (without shoes).
- Obtain blood samples for the following: \*
  - Routine hematology and chemistry (see [Table 2](#))
  - Serum pregnancy test (only for female subjects who have reached menarche)
- Obtain urine samples for urinalysis.\*
- Perform alcohol test and urine drug screens.\*
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.

\* Subjects who re-enroll within 2 weeks of Visit 15 do not need clinical labs, drug screen, alcohol test, or serum pregnancy test at the Part 2 Screening.

## 7.6.2 Part 2 Visits for Subjects Re-enrolling Who Do Not Require Titration

Subjects who re-enroll after completing Part 1 do not require titration if they have continued to take Xyrem and are on a stable dose.

### 7.6.2.1 Visit 18 (Onsite) Subjects Re-enrolling Who Do Not Require Titration

- Review the inclusion/exclusion criteria for Part 2 to determine the subject's eligibility to continue participating in the study.
- Record height and weight in ordinary indoor clothes (without shoes).
- Perform alcohol test and urine drug screens.
- Obtain urine sample for pregnancy test (only perform for female subjects who have reached menarche).
- Obtain vital signs (systolic and diastolic blood pressure, pulse/heart and respiratory rate, and body temperature) after the subject has been resting for at least 5 minutes.
- Record all AEs that occur after assent was given and the ICF was signed on the AE CRF.
- Record all concomitant medications that were taken after assent was given and the ICF was signed on the concomitant medications CRF.
- Dispense study drug. (Access IRT.) Provide instructions for dose administration and, if flavored diluent is requested and available, the preparation of study drug with flavored diluent to subjects/parent(s)/guardian(s). See [Section 6.10](#).
- Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur **prior to** the subject's 18<sup>th</sup> birthday.

### 7.6.2.2 Visits 19 through 42 for Subjects Who Do Not Require Titration

Follow the activities in [Sections 7.5.2](#) through [7.5.5](#).

## 7.6.3 Part 2 Visits for Subjects Re-enrolling Who Require Titration

### 7.6.3.1 Visit 18 (Onsite) Subjects Re-enrolling Who Require Titration – Begin Titration (Week T1)

Titration is required for subjects who are re-enrolling after completing Part 1 of the study and have been off Xyrem for  $\geq 1$  month. For subjects who have been off Xyrem for less than 1 month, titration may also be required per the Investigator's judgment. Subjects will be titrated to Xyrem as described in [Section 3.1.2](#). The Part 2 Titration may last up to 10 weeks. Once it is determined that the subject has achieved clinical benefit in cataplexy and EDS while maintaining tolerability, the subject may remain on that stable dose through the remainder of the titration period. However, Xyrem dose adjustment due to tolerability and efficacy is permitted per the Investigator's judgment.

Follow the activities in [Section 7.6.2.1](#).

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#### 7.6.3.2 Visits 18.1, 18.2, 19, 19.1, 20, 20.1 (Phone Calls) Subjects Re-enrolling Who Require Titration

Study activities for Titration Phone Visits 18.1 (Week T2 +3 days), 18.2 (Week T3 +3 days), 19 (Week T4 +3 days), 19.1 (Week T7 +3 days), 20 (Week T8 +3 days), 20.1 (Week T10 +3 days) are as follows:

- Record all AEs that occur after assent was given and the ICF was signed on the AE CRF.
- Record all concomitant medications that were taken after assent was given and the ICF was signed on the concomitant medications CRF.
- Determine if additional dose titration is necessary.
- Determine when the subject will be 18 years of age. Schedule the Part 2 Study Termination Visit to occur *prior to* the subject's 18th birthday.

#### 7.6.3.3 Visits 21 through 42 for Subjects Who Require Titration

Follow activities in [Sections 7.5.2](#) through [7.5.5](#).

## 8 QUALITY CONTROL AND ASSURANCE

The study will be conducted according to GCP guidelines and according to local and national law. Quality audits may be performed at the discretion of Jazz Pharmaceuticals or its designee.

## 9 PLANNED STATISTICAL METHODS

### 9.1 General Considerations

The primary objectives of this study are to evaluate the efficacy and safety of Xyrem in the treatment of cataplexy in narcolepsy in pediatric subjects. Secondary objectives are to evaluate the efficacy of Xyrem in the treatment of EDS in pediatric subjects with narcolepsy with cataplexy, to characterize the PK of Xyrem given as two doses to children and adolescents (ages 7-17 years) with narcolepsy with cataplexy, and to evaluate the safety of titrating Xyrem in children and adolescents to an effective and tolerable dose.

Non-categorical efficacy parameters will be analyzed by non-parametric analysis of covariance (ANCOVA). Ordinal categorical parameters, including CGIc and PGIC, will be analyzed using Cochran–Mantel–Haenszel (CMH) tests for row mean score difference. PK parameters will be assessed by analysis of variance (ANOVA) models using natural log-transformed data. Safety data will be summarized using descriptive statistics. When data are reported by age group, either ages 7-11 years or ages 12-17 years, subjects will be summarized by age at Visit 2 (start of the Stable-Dose Period) for subjects on Xyrem at study entry and at Visit 1.1 (start of the Titration Period) for Xyrem-naïve subjects.

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## 9.2 Determination of Sample Size

The study will enroll pediatric subjects who are diagnosed with narcolepsy with cataplexy and who are between 7 and 16 years of age, inclusive, to ensure subjects are <18 years of age at the end of Part 1 of the study. At least 100 subjects will be enrolled in the study to assess the safety of Xyrem in this pediatric population.

Prior to Amendment 4, a sample size of 70 subjects was planned to enter the randomized-withdrawal (Double-Blind Treatment) period. This sample size was estimated based on repeated resampling of the data with replacement (bootstrapping) from previous narcolepsy trials in adults (GHB-2 and OMC-SXB-15). The analysis showed that a sample of 35 subjects on Xyrem (sodium oxybate) treatment had at least 40% difference from endpoint to baseline in the mean weekly number of cataplexy attacks, as a percentage of endpoint, over 95% of the time. The present study (13-005) differs from Studies GHB-2 and OMC-SXB-15 in that pediatric subjects will be enrolled instead of adults, the study design is randomized-withdrawal versus a standard randomized treatment study, and the length of the randomized period is 2 weeks for 13-005 versus 4 weeks for GHB-2 and 8 weeks for OMC-SXB-15. Discounting for these factors, a sample of 35 subjects in each arm was expected to have at least 80% power to detect a difference between the two treatment groups of 40% in the percentage change in the mean weekly number of cataplexy attacks during the 2-week Double-Blind Treatment Period of the study as compared with the mean weekly number of cataplexy attacks during the last 2 weeks of the immediately preceding stable-dose period, using a two-sided alpha of 0.05.

Every effort will be made to enroll approximately 30 subjects on Xyrem at study entry of the anticipated 100 subjects enrolled. Other subjects enrolled will be Xyrem naïve at study entry.

A subset of the subjects who are taking Xyrem at a stable dose for their narcolepsy symptoms will participate in the PK evaluation. Up to 18 subjects in each of the two age groups (7-11 year olds and 12-17 year olds) will be enrolled to ensure a minimum of 12 completers in each age group. If the variability of PK data in children and adolescents is comparable to that of adults, a sample size of 12 completers in each age group is expected to provide adequate precision to characterize the PK of sodium oxybate in each age group. However, when sufficient data are obtained to characterize the PK profile with adequate precision during the study, as determined by the Data and Safety Monitoring Board (DSMB), or when enrollment of 100 subjects in the study has been reached, enrollment for the PK evaluation will stop and available data will be used for analysis.

## 9.3 Analysis Populations

The Safety Population will consist of all subjects who are dispensed study drug. This population will be used for tables and listings of safety data. This population will also be used to summarize efficacy data as appropriate. The Safety Population will be additionally categorized by period and by whether the subject took study drug during the different study periods.

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The PK Half-Dose Population will consist of all subjects who have any PK data for PK Night 1 when subjects receive one half of their usual stable dose. This population will be used for listings and descriptive statistics of the half-dose PK data.

The PK Full-Dose Population will consist of all subjects who have any PK data for PK Night 2 when subjects receive their usual stable dose. This population will be used for listings and descriptive statistics of the full-dose PK data.

The PK Completer Population will consist of all subjects who have PK data for both PK nights. This population will be used for evaluating within subject dose proportionality.

The Efficacy Population will consist of all subjects who are randomized to Xyrem or Xyrem placebo and who complete at least 5 days of dosing in the Double-Blind Treatment Period. This population will be used as the main analysis population for tables of the primary and secondary efficacy endpoints.

The Randomized Population will consist of all subjects who are randomized to Xyrem or Xyrem placebo for the Double-Blind Treatment Period of the study. This population will be used to summarize exposure to double-blind treatment. This population may also be used for summaries of safety data specific to the Double-Blind Treatment Period. This population may also be used for an additional analysis of the primary and/or secondary efficacy endpoints.

The Continued Access Population will consist of all subjects who took study drug in Part 2. This population will be used for tables and listings of Part 2 data.

#### **9.4 Demographics and Baseline Characteristics**

Demographics and baseline characteristics will be summarized for the safety population, the PK half-dose population, the PK completer population, the randomized population, the efficacy population, and the continued access population. The summaries of data will include numbers and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables. Tables for the randomized population and the efficacy population will be by randomized treatment group (Xyrem or Xyrem placebo) and overall. The randomized population tables will include a comparison of the treatment groups, with categorical variables analyzed using a chi-square test and continuous variables analyzed using a one-way analysis of variance (ANOVA) model with treatment as the only factor.

#### **9.5 Handling of Dropouts and Missing Data**

The following methods will be used to handle missing efficacy data and data from subjects who discontinue early in the Double-Blind Treatment Period. The weekly number of cataplexy attacks will be computed as the average from days with non-missing data, multiplied by 7. School attendance will be calculated as the number of missed days, multiplied by 100, divided by the actual number of school days (not including holidays) up to the point of Part 1 early termination or Double-Blind Treatment Period completion. The last post Stable-Dose Period assessment of all other measures will be used as the end of the Double-Blind Treatment Period assessment.

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## 9.6 Efficacy Endpoints

All efficacy assessments will be comparisons of the measurement made during, or at the end of, the last 2 weeks of the Stable-Dose Period compared with the 2 weeks of Double-Blind Treatment Period.

Primary endpoint:

1. Change in weekly number of cataplexy attacks

Key secondary endpoints:

2. CGIc for cataplexy severity
3. Change in the ESS (CHAD) score

Other secondary endpoints:

4. CGIc for narcolepsy overall
5. Change in Quality of Life (QoL) (SF-10)

Exploratory endpoints:

6. Change in weekly school attendance (if enrollment overlaps with school attendance period)
7. PGIC for narcolepsy overall

### 9.6.1 Statistical Analysis

#### To address Primary Objective 1 and Secondary Objective 1:

A tiered approach was planned to control the Type 1 family-wise error rate at the 0.05 significance level with all tests being two-sided for testing of the primary and secondary efficacy endpoints.

Due to the positive primary efficacy results from the pre-specified interim analyses (described in [Section 9.8](#)), the DSMB recommended to stop the Double-Blind Randomized-Withdrawal Period. Tiered testing on secondary endpoints, as defined below, will be conducted with a significance level of 0.05, with all tests being two-sided.

Tier 1: Primary endpoint

1. Change in weekly number of cataplexy attacks from the last 2 weeks of the Stable-Dose Period to the 2 weeks of the Double-Blind Treatment Period.

The primary endpoint demonstrated efficacy at the interim analysis with a significance level <0.005. Testing will continue with Tier 2.

Tier 2: Key secondary endpoint #2

2. CGIc for cataplexy severity from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period

The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 3 tests will be conducted.

Tier 3: Key secondary endpoint #3

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3. Change in the ESS (CHAD) score from the end of the Stable-Dose Period to the end of Double-Blind Treatment Period

The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 4 tests will be conducted.

Tier 4: Other secondary endpoints #4

4. CGIc for narcolepsy overall from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period

The testing of this endpoint will be conducted at the 0.05 significance level. If Xyrem is significantly better than placebo at this level, Tier 5 tests will be conducted.

Tier 5: Other secondary endpoint #5

5. Change in QoL (SF-10) from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period

The testing of this endpoint will be conducted at the 0.05 significance level.

Exploratory efficacy endpoints will be tested without multiplicity adjustments. For these parameters, nominal p-value will be reported.

Non-categorical efficacy parameters will be analyzed by non-parametric analysis of covariance (ANCOVA). Ordinal categorical parameters, including CGIc and PGIC, will be analyzed using Cochran–Mantel–Haenszel (CMH) tests for row mean score difference.

Efficacy data in the open-label phase will be summarized by visit.

## 9.7 Statistical Analysis of Pharmacokinetic Variables

**To address Secondary Objective 2:** Concentration data for sodium oxybate will be summarized by sampling time point and by PK parameter using descriptive statistics for each age group and overall. Dose proportionality will be assessed from the ratio of AUC and  $C_{max}$  values. The ratios and their 90% confidence intervals will be presented. If warranted, regression models will be used to explore the relationship between plasma concentration and dose on a mg/kg basis.

## 9.8 Interim Analysis

A preplanned interim analysis was conducted after 35 subjects completed or discontinued early from the Double-Blind Treatment Period. The interim analysis was performed by a statistician not directly involved with the design and analysis of the study. The data were reviewed by a DSMB that recommended stopping placebo treatment in the Double-Blind Randomized-Withdrawal Period and continue the study as an open-label safety study because of positive efficacy results.

Considerations for stopping the study early included the following as initially planned. Given now the placebo treatment is stopped after the interim analysis review by DSMB, the DSMB will continue to review safety and PK data as outlined below.

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**For stopping the study early because of treatment success**, so that fewer subjects will be exposed to placebo: The O'Brien-Fleming approach will be used with the primary efficacy endpoint. This endpoint will be tested at a significance level of 0.005 at the interim analysis. If statistical significance is shown, the DSMB may recommend stopping the study considering the overall study objectives and subject's safety. If the study is not stopped, to maintain an overall alpha of 0.05, the final analysis will be conducted at a significance level of 0.048, based on one prior look at the data.

**For stopping the study early because of treatment failure:** In the interim analysis, if the null hypothesis for the primary efficacy endpoint is not rejected at the 0.005 significance level, then a futility analysis will be conducted. The conditional power approach will be used. Assuming the trend in the data observed up to the interim analysis will continue for the data collected between the interim analysis and the final analysis, the conditional power of rejecting the null hypothesis at the final analysis will be calculated. If the conditional power is less than 15%, it will be concluded that the study is unlikely to demonstrate efficacy and the DSMB may recommend stopping the study considering the overall study objectives and subject's safety. The study may be discontinued early due to futility.

**For stopping the study early because of safety reasons:** Safety data, including the incidence of adverse events, will be reviewed by the DSMB at regular intervals. Any serious adverse events or deaths will be given detailed attention. Taking all data reviewed into account, the DSMB will determine if the risk to subjects warrants study discontinuation.

An ongoing analysis of the PK data will also be conducted to determine if a sufficient number of samples have been collected to adequately characterize the PK of Xyrem in children and adolescents.

## 9.9 Safety Analysis

Safety will be assessed at time points specified in the schedules of events, as well as throughout the study. Safety assessments will include the following:

- Adverse event (AE) monitoring
- Vital signs
- Physical examinations (including weight and height)
- 12-lead ECG
- PSG parameters (including respiratory measures)
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Assessments of growth and precocious puberty
- C-SSRS (Children's Since Last Visit version for subjects under 12 years of age and the Since Last Visit version for subjects 12 years of age and older) for emergent suicidality
- CDI 2:SR[S] for emergent or worsening depression
- MASC-10 for emergent or worsening anxiety
- Serum pregnancy tests (if applicable)

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Exploratory endpoint:

- CO<sub>2</sub> monitoring (EtCO<sub>2</sub> or TcCO<sub>2</sub>) in sites where monitoring is routinely performed and performance will not negatively impact study participation or PSG data integrity

A DSMB will review the safety data on a regular basis, including monitoring for the following AEs:

- Confusion
- Somnolence and more pronounced levels of depressed consciousness
- Respiratory depression
- Depressed mood and suicidality
- Anxiety
- Sleepwalking and other parasomnias
- Abuse and misuse of study drug
- Weight loss

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA).

**To address Primary Objective 2 and Secondary Objective 3:** Safety will be summarized using descriptive statistics and reported separately for Part 1 and Part 2 as well as across the entire study (Part 1 and Part 2) for select analyses. Adverse events will be assessed for subpopulations including Xyrem naïve, subjects on Xyrem at study entry, Ages 7-11, and Ages 12-17, as applicable. When summarizing data across the entire study by subpopulations, subjects are analyzed according to their initial enrollment status. For Part 1, adverse events will also be summarized by treatment group and by dose. Safety analyses will also include an analysis of the nadir oxygen saturation level at each dose, and number and duration of any confirmed desaturations below 90%, 80%, 70%, 60% and 50% on PSG nights excluding the screening PSG. For Part 2, safety data will be summarized by Ages 7-11, Ages 12-17, and overall.

## 10 DATA QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data will be reviewed for accuracy and completeness by Jazz Pharmaceuticals or its representatives during and after onsite monitoring visits, and any discrepancies will be resolved with the Investigator or designees as appropriate.

### 10.1 Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures (SOPs) of Jazz Pharmaceuticals or the Contract Research Organization (CRO). Data will be managed in accordance with the privacy regulations of the prevailing region. A comprehensive Data Management Plan (DMP) will be developed, including but not limited

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to a Data Management Overview, Database Contents, annotated CRF, Pre-Entry Review List, Self-Evident Correction Conventions, Query Contacts, and Consistency Checks.

## 10.2 Case Report Forms

Jazz Pharmaceuticals or its designee will supply CRFs for the recording of all study data not recorded in subject diaries, ECG, or generated by laboratory report. All data recorded in the CRFs must be completed in the electronic case report forms (eCRFs).

The Principal Investigator must review the CRFs and provide his/her signature certifying that he/she has reviewed the data and considers the data accurate to the best of his/her knowledge. Regardless of who signs or completes the forms, it is the Principal Investigator's responsibility to ensure the accuracy of the forms.

## 10.3 Retention of Data

The investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Study (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Jazz Pharmaceuticals. It is the responsibility of Jazz Pharmaceuticals to inform the Investigator/institution when these documents no longer need to be retained.

## 10.4 Data and Safety Monitoring Board (DSMB)

The DSMB will review the safety data on a regular basis and data from the Interim Analysis (see [Section 9.8](#)).

## 10.5 Panel of Narcolepsy Experts

A panel of narcolepsy experts may be convened to confirm the diagnosis of narcolepsy with cataplexy in accordance with ICSD-3 if a subject is not positive for the Human Leukocyte Antigen (HLA) DQB1:0602 haplotype, determined prior to the study or as part of the study screening procedures, and does not have a CSF hypocretin level  $\leq 110$  pg/mL determined prior to the study.

The membership and the primary responsibilities of the panel will be defined in a charter that will also provide procedures for case review, documentation, and communication of decisions.

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## 11 ADMINISTRATIVE CONSIDERATIONS

### 11.1 Investigators and Study Administrative Structure

#### 11.1.1 Contract Research Organization

[REDACTED]

#### 11.1.2 Sponsor's Medical Monitor

[REDACTED]

#### 11.1.3 EU Medical Monitor

Contact information for the EU Medical Monitor will be provided separately.

#### 11.1.4 Investigator

Multicenter

#### 11.1.5 Clinical Laboratory

[REDACTED]

#### 11.1.6 Bioanalytical Laboratory

[REDACTED]

### 11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The final approved protocol and the informed consent form will be reviewed by the IRB/IEC. In addition, the IRB/IEC will review any other written information to be provided to the subject, advertisements for subject recruitment (if used), and subject compensation (if any). The committee's decision concerning conduct of the study will be sent in writing to the

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Investigator and a copy will be forwarded to Jazz Pharmaceuticals. The Investigator agrees to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening problems, death, or any significant protocol deviations.

A list of the IRB/IEC members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an IRB/IEC assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on IRB/IEC letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the informed consent form was also reviewed.

A clinical study may not be initiated before the proposed protocol and informed consent form have been reviewed and unconditionally approved by an IRB/IEC meeting federal regulations. The clinical study remains subject to continuing review by the IRB/IEC. Jazz Pharmaceuticals or its designee will supply all necessary data for the Investigator to submit to the IRB/IEC. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval from the site's IRB/IEC has been received by Jazz Pharmaceuticals.

The Investigator is responsible for ensuring initial and continued review and approval of the clinical study by the IRB/IEC at his/her site. The Investigator must also ensure that he/she will promptly report to the IRB/IEC and Jazz Pharmaceuticals all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he/she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to human subjects. If the study remains in progress for more than 1 year, documentation of annual renewal must be submitted to Jazz Pharmaceuticals or its designee. Within 3 months of study completion or termination, a final report must be provided to the IRB/IEC by the clinical site.

### **11.3 Form FDA 1572**

The investigator must sign a completed Form FDA 1572 before initiation of the study and provide the original hand-signed and hand-dated document along with the appropriate curriculum vitae to Jazz Pharmaceuticals or its designee.

### **11.4 Ethical Conduct of the Study**

The study will be conducted in accordance with regulations relating to GCP and the standard operating procedures (SOPs) of the CRO and Jazz Pharmaceuticals. These standards respect the following guidelines:

- Good Clinical Practice: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (Title 21 CFR Parts 11, 50, 54, 56, 312, and 314).

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- Current Declaration of Helsinki, concerning medical research in humans (“WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects,” Fortaleza, Brazil 2013).

### **11.5 Subject Information Assent and Consent**

All subjects will provide assent and their parent(s) or guardian(s) will give written informed consent in accordance with local IRB/IEC requirements before the performance of any study related procedures.

Each subject’s chart will have the assent of the subject documented (written or verbal) and the ICF signed by the parent or guardian for study participation, and for PK evaluation if applicable, attached to it. When the study treatment is completed and the CRF has been monitored, the ICF will be kept in the investigator’s central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the performance of the study.

### **11.6 Subject Confidentiality**

All reports and communications relating to the subjects in the study will identify each subject only by his/her initials and by the subject’s study number or as required by regional or national regulations. These documents will be treated with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

Portions of the subject’s medical records pertinent to the study will be reviewed by Jazz Pharmaceuticals personnel or its designee and possibly by governmental agency personnel to ensure adequate source documentation, accuracy, and completeness of the CRFs. The IRB has the authority to review subject records.

### **11.7 Protocol Adherence – Amendments**

The protocol must be read thoroughly and the instructions must be followed exactly.

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the Investigator and the Jazz Pharmaceuticals designees. The IRB/IEC will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/IEC approval has been received.

If a country or region specific amendment is required based on local regulation, the amendment will be submitted to the IRB(s) and competent authority of that country or region only.

### **11.8 Required Documents**

The Investigator must provide Jazz Pharmaceuticals or its designee with the applicable regulatory documents before the enrollment of any subject (copies should be kept by the Investigator in the Investigator’s regulatory document binder).

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## 11.9 Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the Investigator. This will include telephone calls and onsite visits. During the onsite visits, the CRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the site. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The Investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

## 11.10 Protocol Deviations

All major protocol deviations must be reported to the IRB in an expedited fashion. It is the responsibility of the principal investigator to ensure proper reporting to the IRB. All protocol deviations (major and minor) must be reported to Jazz Pharmaceuticals or designee.

## 11.11 Retention of Data

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Trial (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Jazz Pharmaceuticals. It is the responsibility of Jazz Pharmaceuticals to inform the investigator/institution as to when these documents no longer need to be retained.

## 11.12 Publication and Disclosure Policy

All information concerning Xyrem, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. CRFs also remain the property of Jazz Pharmaceuticals. The investigator agrees to use this information only to complete this study and will not use it for other purposes without the written consent

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of Jazz Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

It is understood by the Investigator that Jazz Pharmaceuticals will use the information obtained in this clinical study in connection with the study of Xyrem, and therefore may disclose this information as required to other Jazz Pharmaceuticals investigators, appropriate international regulatory agencies, or others. In agreeing to participate in this study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the Investigator and/or institution. It is intended that the results of this study may be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

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## Appendix 1 Schedule of Events—Subjects on Xyrem at Study Entry

### Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Safety Period—Subjects on Xyrem at Study Entry

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment*	End Double-Blind*/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
					V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	
Visits	V1 Day -30 to -1 <sup>a,b</sup>	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	V16 <sup>d</sup> 14 days after last treatment +3 days
Informed Consent/Assent	X															
Inclusion/Exclusion Criteria	X	X														
Demographics and Contact Information	X															
Medical History including narcolepsy history, usual bedtime and awakening time	X															
Physical Examination including a brief neurological exam	X			X											X	
Tanner Stage Assessment	X														X	
Height	X	X	X	X	X		X		X			X			X	X
Weight	X	X	X	X	X		X		X			X			X	X
Vital Signs <sup>e</sup>	X	X	X	X	X		X		X			X			X	X

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**Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Safety Period—Subjects on Xyrem at Study Entry**

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment*	End Double-Blind*/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
					V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	
Visits	V1 Day -30 to -1 <sup>a,b</sup>	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	V16 <sup>d</sup> 14 days after last treatment +3 days
Pulse Oximetry on room air while fully awake	X															
HLA DQB1:0602 <sup>f</sup>	X															
Hematology, Chemistry <sup>g</sup>	X			X											X	
TSH	X															
<b>PK subjects only:</b> Coagulation <sup>h</sup>	X <sup>i</sup>															
Urinalysis	X			X											X	
<b>Only for Girls &lt;8 years:</b> estradiol, LH, FSH <b>Only for Boys &lt;9 years:</b> testosterone, LH, FSH	X														X	
Urine Drug Screen	X	X		X <sup>j</sup>	X		X		X			X			X	
Alcohol Test	X	X		X <sup>j</sup>	X		X		X			X			X	
Serum Pregnancy	X			X												
Urine Pregnancy		X													X	
12-Lead ECG	X			X											X	

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**Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Safety Period—Subjects on Xyrem at Study Entry**

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment*	End Double-Blind*/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
					V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	
Visits	V1 Day -30 to -1 <sup>a,b</sup>	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	V16 <sup>d</sup> 14 days after last treatment +3 days
Cataplexy Frequency Diary <sup>k</sup>																
CGIs for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment	X <sup>1</sup>															
CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment	X <sup>1</sup>															
CGIs (narcolepsy overall)	X	X	X													
CGIs (cataplexy severity)	X	X	X													
PGIc (narcolepsy overall)				X												
CGIc (narcolepsy overall)				X												
CGIc (cataplexy severity)				X												
ESS (CHAD)	X	X	X	X	X		X		X			X			X	

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**Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Safety Period—Subjects on Xyrem at Study Entry**

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment*	End Double-Blind*/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
					V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	
Visits	V1 Day -30 to -1 <sup>a,b</sup>	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	V16 <sup>d</sup> 14 days after last treatment +3 days
Study Drug Dosing Diary <sup>k</sup>																
Stimulant Dosing Diary <sup>k</sup>																
Review subject dosing diaries for compliance																
Review cataplexy frequency diary																
SF-10		X	X	X	X		X		X			X			X	
C-SSRS for suicidality <sup>m</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDI2:SR[S] for depression	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MASC-10 for anxiety scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
School Attendance Diary <sup>n</sup>																
AE Reporting																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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**Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Safety Period—Subjects on Xyrem at Study Entry**

	Screening Visit	Start Stable-Dose	End Stable-Dose/ Begin Double-Blind Treatment*	End Double-Blind*/ Begin Open-Label Safety	Open-Label Safety Period with Xyrem											Safety Follow-up
					V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	
Visits	V1 Day -30 to -1 <sup>a,b</sup>	V2 Day 1	V3 Week 3 ± 3 days	V4 Week 5 +3 days	V5 Week 9 ±7 days	V6 W 16 ±7 days Phone call	V7 W 18 ±7 days	V8 W 22 ±7 days Phone call	V9 W 26 ±7 days	V10 W 30 ±7 days Phone call	V11 W 34 ±7 days Phone call	V12 W 39 ±7 days	V13 W 43 ±7 days Phone call	V14 W 48 ±7 days Phone call	Visit 15 <sup>c</sup> W 52 ±7 days Or Part 1 Early Termination	V16 <sup>d</sup> 14 days after last treatment +3 days
Dispense Study Drug <sup>o</sup>		X	X	X	X		X		X			X				
Collect study drug, measure compliance			X	X	X		X		X			X			X	
Fasting morning blood sample: GH, IGF-1, prolactin			X	X											See Appendix 1.2 <sup>P</sup>	
Breakfast			X	X											See Appendix 1.2 <sup>P</sup>	
PSG	See Appendix 1.2														See Appendix 1.2 <sup>P</sup>	
<b>PK subjects only:</b> PK Nights 1 and 2		When the subject is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit. See Appendix 3														

An arrow (  ) indicates that the assessment is continuous.

\* **Subjects who enter the Double-Blind Period after Amendment 4 becoming effective will receive open-label Xyrem during the Double-Blind Period.**

- a) All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. If needed, additional screening time may be granted with permission of the

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Medical Monitor.

- b) The Screening Period for subjects with low body weight who are participating in the PK evaluation should be as close as possible to 30 days to minimize the amount of blood drawn over 30 days.
- c) If the subject is continuing directly into Part 2, see [Appendix 22](#).
- d) Do not complete the Safety Follow-up visit for subjects who continue directly into Part 2 (see Appendix 22).
- e) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for  $\geq 5$  min.
- f) HLA DQB1:0602: Collect blood sample unless previous result available.
- g) See [Table 2](#).
- h) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).
- i) Collect coagulation samples within 30 days prior to PK Night 1. PK evaluation will occur at any time while subjects are on a stable dose of Xyrem.
- j) Urine drug screen and alcohol test: only for subjects continuing to the Open-label Safety Period.
- k) Recorded daily in electronic diary.
- l) Impression of severity prior to any narcolepsy treatment.
- m) C-SSRS: Use Baseline/Screening Version at Visit 1 and Since Last Visit version at all other visits for subjects  $\geq 12$  years of age, and use Children's versions for children  $< 12$  years of age.
- n) School attendance collected for subjects who attend school during Stable-Dose and Double-Blind Treatment Periods.
- o) Study drug quantities dispensed at study visits in accordance with protocol and as required by State or local regulation.
- p) If the subject withdraws early from the study during the Open-Label Safety Period, perform a PSG if subject is willing and if the subject is willing to be dosed with study drug for this PSG night. Part 1 early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.

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## Appendix 1.2 PSG Night Procedures– Subjects on Xyrem at Study Entry

	Part 1 Screening Visit	Open-Label Safety Period with Xyrem
Visits	V1 Day -30 to -1 <sup>a</sup>	Visit 15 Week 52 (±7 days) Or Part 1 Early Termination
<b>PSG Night Procedures<sup>b</sup></b>	Screening PSG	End of Study (Part 1) PSG /Part 1 Early Termination
Review inclusion/exclusion criteria	X	
Light dinner >2 hours before dosing	X <sup>c</sup>	X <sup>c</sup>
Confirm Parent(s)/ Guardian(s) Contact Information	X	X
Administer or supervise the administration of Study Drug <sup>d</sup>	X	X
PSG	X	X <sup>e</sup>
EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>f</sup>	X	X
Vital Signs <sup>g</sup>	X	X
Pulse Oximetry <sup>h</sup>	X	X
Record AEs/Concomitant Medications	X	X
Brief neurological exam <sup>i</sup>	X	X
<u>Fasting morning blood sample</u> : GH, IGF-1, prolactin		X
Breakfast (if subject prefers to eat at the study center)	X	X

- a) If needed, additional screening time may be granted with permission of the Medical Monitor.
- b) Perform all other procedures for the visit prior to the PSG night procedures.
- c) Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or home.
- d) Administer the subject's nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
- e) Part 1 Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
- f) CO<sub>2</sub> monitoring on PSG nights only at sites where monitoring is routinely performed.
- g) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min. Obtain at pre-dose and before release from study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the 1<sup>st</sup> Xyrem dose, heart and respiratory rates recorded via PSG.
- h) SpO<sub>2</sub> monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
- i) Brief neurological exam before discharge on the morning after PSG.

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## Appendix 2 Schedule of Events–Xyrem-Naïve Subjects at Study Entry

### Appendix 2.1 Part 1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind Treatment Period– Xyrem-Naïve Subjects at Study Entry

Events	Screening	Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period*	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
		Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment*	End of Double-Blind Treatment* Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1 <sup>a</sup>	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Informed Consent/Assent	X											
Inclusion/exclusion Criteria	X	X										
Demographics and Contact Information	X											
Medical History including narcolepsy history, usual bedtime and awakening time	X											
Physical Examination including a brief neurological exam	X										X	
Tanner Stage Assessment	X											
Height	X	X	X			X		X	X	X	X	X
Weight	X	X	X			X		X	X	X	X	X
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) <sup>b</sup>	X	X	X			X		X	X	X	X	X

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**Appendix 2.1 Part 1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind Treatment Period– Xyrem-Naïve Subjects at Study Entry**

Events	Screening	Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period*	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
		Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment*	End of Double-Blind Treatment* Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1 <sup>a</sup>	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Pulse Oximetry on room air while fully awake	X											
HLA DQB1:0602 <sup>c</sup>	X											
Hematology, Chemistry <sup>d</sup>	X										X	
TSH	X											
Urinalysis	X										X	
<b>Only for Girls &lt;8 years:</b> Estradiol, LH, FSH <b>Only for Boys &lt;9 years:</b> Testosterone, LH, FSH	X											
Urine Drug Screen	X	X									X <sup>e</sup>	
Alcohol Test	X	X									X <sup>e</sup>	
Serum Pregnancy Test	X										X	
Urine Pregnancy test		X										
12 Lead ECG	X										X	
Cataplexy Frequency Diary <sup>f</sup>			→									
CGIs for Historical Narcolepsy Overall Severity Prior to any	X <sup>g</sup>											

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## Appendix 2.1 Part 1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind Treatment Period– Xyrem-Naïve Subjects at Study Entry

Events	Screening	Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period*	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
		Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment*	End of Double-Blind Treatment* Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1 <sup>a</sup>	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
Narcolepsy Treatment												
CGIs for Historical Cataplexy Severity Prior to any Narcolepsy Treatment	X <sup>g</sup>											
CGIs (narcolepsy overall)	X	X								X		
CGIs (cataplexy severity)	X	X								X		
PGIc (narcolepsy overall)											X	
CGIc (narcolepsy overall)											X	
CGIc (cataplexy severity)											X	
ESS (CHAD)	X	X								X	X	
Study Drug Dosing Diary <sup>f</sup>												→
Stimulant Dosing Diary <sup>f</sup>												→
Review subject dosing diaries for compliance and cataplexy frequency diary												→
SF-10		X								X	X	
C-SSRS for suicidality <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X
CDI2:SR[S] for depression	X	X	X	X	X	X	X	X	X	X	X	X
MASC-10 for anxiety scale	X	X	X	X	X	X	X	X	X	X	X	X

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### Appendix 2.1 Part 1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind Treatment Period– Xyrem-Naïve Subjects at Study Entry

Events	Screening	Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period*	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
		Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment*	End of Double-Blind Treatment* Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call W2	V1.4 Phone Call W3	V1.5 W4	V1.6 Phone Call W6	V1.7 W8	V2	V3	V4	
Weeks (W)	Day -30 to -1 <sup>a</sup>	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
School Attendance Diary <sup>i</sup>												→
Assess subject and determine if additional dose titration is necessary			X	X	X	X	X	X				
AE Reporting												→
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
<b>PK subjects only:</b> Coagulation									X <sup>j</sup>			
Dispense Study Drug <sup>k</sup>		X	X			X		X	X	X	X	
Collect study drug, measure compliance			X			X		X	X	X	X	
Fasting morning blood sample: GH, IGF-1, prolactin <sup>l</sup>										See Appendix 2.3	X	
Breakfast										See Appendix 2.3	X	
PSG	See Appendix 2.3									See Appendix 2.3		

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**Appendix 2.1 Part 1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind Treatment Period– Xyrem-Naïve Subjects at Study Entry**

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period*	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration						End Titration	End of Stable-Dose	End of Double-Blind Treatment*		
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1 <sup>a</sup>	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
PK Evaluation									When the subject is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit. See Appendix 3.			

An arrow ( → ) indicates that the assessment is continuous.

Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

\* **Subjects who enter the Double-Blind Period after Amendment 4 becoming effective will receive open-label Xyrem during the Double-Blind Period.**

- a) All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Screening Visit (Visit 1) starts when a subject is assigned a subject number via IVRS/IWRS. If needed, additional screening time may be granted with permission of the Medical Monitor.
- b) Obtain vital signs after subject has been resting for ≥5 min.
- c) HLA DQB1:0602: Collect blood sample unless previous result available.
- d) See Table 2.
- e) Urine drug screen and alcohol test: only for subjects continuing into the Open-Label Safety Period.
- f) Recorded daily in electronic diary.
- g) Impression of severity prior to any narcolepsy treatment.
- h) C-SSRS: Use Baseline/Screening Version at Visit 1 and Since Last Visit version at all other visits for subjects ≥12 years of age and use Children’s versions for children <12 years of age.
- i) School attendance collected for subjects who attend school during Stable-Dose and Double-Blind Treatment Periods.

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- j) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT). Collect coagulation samples within 30 days prior to PK Night 1. PK evaluation will occur at any time while subjects are on a stable dose of Xyrem.
- k) Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.
- l) See [Table 6](#).

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## Appendix 2.2 Part 1 Open-Label Safety Period–Xyrem-Naïve Subjects at Study Entry

Events	Open-Label Safety Period with Xyrem											Safety Follow-up
	V5 <sup>a</sup> (4 weeks after end of Double-Blind Treatment Period) ±7 days	V6 W 16 Phone Call ±7 days	V7 W18 ±7 days	V8 W22 ±7 days Phone call	V9 Week 26 ±7 days	V10 W30 ±7 days Phone call	V11 Week 34 ±7 days Phone call	V12 Week 39 ±7 days	V13 Week 43 ±7 days Phone call	V14 Week 48 ±7 days Phone call	Visit 15 <sup>b</sup> Week 52 ±7 days Or Part 1 Early Termination	V16 <sup>c</sup> 14 days after last treatment +3 days
Physical Examination including brief neurological exam											X	
Tanner Stage Assessment											X	
Height	X		X		X			X			X	X
Weight	X		X		X			X			X	X
Chemistry, Hematology											X	
Urinalysis											X	
Only for Girls <8 years: Estradiol, LH, FSH Only for Boys <9 years: Testosterone, LH, FSH											X	
Urine Drug Screen	X		X		X			X			X	
Alcohol Test	X		X		X			X			X	
Urine Pregnancy test											X	
Study Drug Dosing Diary <sup>d</sup>	→											
12-Lead ECG											X	
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) <sup>e</sup>	X		X		X			X			X	X
Cataplexy frequency diary <sup>d</sup>	→											
ESS (CHAD)	X		X		X			X			X	
C-SSRS <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X

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## Appendix 2.2 Part 1 Open-Label Safety Period–Xyrem-Naïve Subjects at Study Entry

Events	Open-Label Safety Period with Xyrem											Safety Follow-up
	V5 <sup>a</sup> (4 weeks after end of Double-Blind Treatment Period) ±7 days	V6 W 16 Phone Call ±7 days	V7 W18 ±7 days	V8 W22 ±7 days Phone call	V9 Week 26 ±7 days	V10 W30 ±7 days Phone call	V11 Week 34 ±7 days Phone call	V12 Week 39 ±7 days	V13 Week 43 ±7 days Phone call	V14 Week 48 ±7 days Phone call	Visit 15 <sup>b</sup> Week 52 ±7 days Or Part 1 Early Termination	V16 <sup>c</sup> 14 days after last treatment +3 days
Depression scale (CDI2:SR[S])	X	X	X	X	X	X	X	X	X	X	X	X
Anxiety scale (MASC-10)	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (SF-10)	X		X		X			X			X	
PSG											See Appendix 2.3 <sup>g</sup>	
AE Reporting	→											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug <sup>h</sup>	X		X		X			X				
Collect trial medicine, measure and review compliance	X		X		X			X			X	
PK evaluation	When the subject is on a stable dose of Xyrem, PK Nights 1 and 2 can be scheduled for a protocol-specified clinic visit or for an additional clinic visit. See Appendix 3.											

An arrow ( → ) indicates that the assessment is continuous.

Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

- Visit 5 will be conducted 4 weeks after the end of the Double-Blind Treatment Period unless Visit 5 is within 2 weeks of the Week 18 visit. Visits 6-16 will be conducted at Weeks 16, 18, 22, 26, 30, 34, 39, 43, 48, 52, and 54 after Day 1.
- If the subject is continuing directly into Part 2, see Appendix 22.
- Do not complete the Safety Follow-up visit for subjects who continue directly into Part 2 (see Appendix 22).
- Recorded daily in electronic diary.
- Obtain vital signs after the subject has been resting for ≥5 minutes.
- C-SSRS: Use Since Last Visit version for subjects ≥12 years of age and use Children's versions for children <12 years of age.
- Part 1 Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
- Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.

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### Appendix 2.3 PSG Night Procedures–Xyrem-Naïve Subjects at Study Entry

	Part 1 Screening Visit	End Stable-Dose Period Begin Double-Blind Treatment Period*	Open-Label Safety Period with Xyrem
Visits	V1 Day -30 to -1 <sup>a</sup>	V3 Week 3 (± 3 days)	Visit 15 Week 52 (±7 days) Or Part 1 Early Termination
PSG Night Procedures <sup>b</sup>	Screening PSG	End of Stable-Dose/Pre-Randomization PSG**	End of Study (Part 1) PSG /Part 1 Early Termination
Review inclusion/exclusion criteria	X		
Light dinner >2 hours before dosing	X <sup>c</sup>	X <sup>d</sup>	X <sup>d</sup>
Confirm Parent(s)/ Guardian(s) Contact Information	X	X	X
Administer or supervise the administration of Study Drug <sup>e</sup>		X	X
PSG	X	X	X <sup>f</sup>
EtCO <sub>2</sub> or TcCO <sub>2</sub> <sup>g</sup>	X	X	X
Vital Signs <sup>h</sup>	X <sup>i</sup>	X <sup>j</sup>	X <sup>j</sup>
Pulse Oximetry	X <sup>k</sup>	X <sup>l</sup>	X <sup>l</sup>
Record AEs/Concomitant Medications	X	X	X
Brief neurological exam <sup>m</sup>		X	X
Fasting morning blood sample: GH, IGF-1, prolactin		X	X
Breakfast (if subject prefers to eat at the study center)	X	X	X

Note: A Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

Note:

\*Subjects who enter the Double-Blind Period after Amendment 4 becoming effective will receive open-label Xyrem treatment during the Double-Blind Period.

\*\*For administrative reasons the terminology for this PSG will retain the reference to “Pre-Randomization”).

- If needed, additional screening time may be granted with permission of the Medical Monitor.
- Perform all other procedures for the visit prior to the PSG night procedures.
- No food restrictions.
- Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or at home.
- Administer the subject’s nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
- Part 1 Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
- CO<sub>2</sub> monitoring on PSG nights only at sites where monitoring is routinely performed.
- Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min.

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- i) Vital signs obtained prior to the start of the PSG and prior to release from study center.
- j) Vital signs obtained at pre-dose and before release from the study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, heart and respiratory rates recorded via PSG.
- k) Monitor SpO<sub>2</sub> to determine obstructive sleep apnea status.
- l) SpO<sub>2</sub> monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
- m) Brief neurological exam before discharge on the morning after PSG.

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### Appendix 3 PK Evaluation Procedures—Subjects Participating in the PK Evaluation

Events/Visits	Prior to PK Night 1	PK Night 1	PK Night 2
Informed Consent/Assent for PK evaluation	X		
Coagulation within 30 days prior to PK Night 1 <sup>a</sup>	X		
Light dinner >2 hours before dosing <sup>b</sup>		X	X
Confirm Parent(s)/Guardian(s) Contact Information		X	X
Blood samples for PK Assessment <sup>c</sup>		X	X
Vital Signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) <sup>d</sup>		X	X
Pulse Oximetry <sup>e</sup>		X	X
Administer or supervise the administration of Study Drug from subject's study drug supply on PK nights		X <sup>f</sup>	X <sup>g</sup>
Brief neurological exam <sup>h</sup>		X	X
Breakfast (if subject prefers to eat at the study center)		X	X

- a) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).
- b) Light dinner taken >2 hours prior to dosing should be the same or similar on both PK Nights. Light meal may be taken at the clinic or at home.
- c) Blood samples for sodium oxybate concentrations will be collected at 0 (pre-dose) and 0.75, 1.5, 2.5, 4 (pre-2nd dose), 4.75, and 8 hours after the first dose. Samples taken within ±5 minutes of the protocol specified time points.
- d) Obtain vital signs after subject has been resting for ≥5 min. Obtain vital signs at pre-dose. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, obtain pulse/heart and respiratory rates.
- e) SpO<sub>2</sub> is monitored continuously from immediately before first dose through 8 hours after the first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. An additional measurement will be taken while the subject is awake and before release from the study center.
- f) Administer ½ of the subject's usual nightly dose in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see [Section 3.1.7](#)).
- g) Administer the subject's nightly dose of Xyrem in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see [Section 3.1.7](#)).
- h) Brief neurological exam before discharge on the morning after pharmacokinetic assessment.

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**Appendix 4      Seattle Children's Hospital and Research Center:  
Maximum allowable blood draw volumes**



# Seattle Children's

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## Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	6.6	300	7.5	15
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11 thru 15	24 thru 33	880-1200	22-30	44-60
16 thru 20	35 thru 44	1280-1600	32-40	64-80
21 thru 25	46 thru 55	1680-2000	42-50	84-100
26 thru 30	57 thru 66	2080-2400	52-60	104-120
31 thru 35	68 thru 77	2480-2800	62-70	124-140
36 thru 40	79 thru 88	2880-3200	72-80	144-160
41 thru 45	90 thru 99	3280-3600	82-90	164-180
46 thru 50	101 thru 110	3680-4000	92-100	184-200
51 thru 55	112 thru 121	4080-4400	102-110	204-220
56 thru 60	123 thru 132	4480-4800	112-120	224-240
61 thru 65	134 thru 143	4880-5200	122-130	244-260
66 thru 70	145 thru 154	5280-5600	132-140	264-280
71 thru 75	156 thru 165	5680-6000	142-150	284-300
76 thru 80	167 thru 176	6080-6400	152-160	304-320
81 thru 85	178 thru 187	6480-6800	162-170	324-340
86 thru 90	189 thru 198	6880-7200	172-180	344-360
91 thru 95	200 thru 209	7280-7600	182-190	364-380
96 thru 100	211 thru 220	7680-8000	192-200	384-400

Based on blood volume of:

1 to 2 kg                      100 mL/kg                      (pre-term infant)

>2 kg                          80 mL/kg                          (term infant - adult)

This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by Rhona Jack, Ph.D. August 2001  
Children's Hospital and Regional Medical Center Laboratory  
Seattle, WA

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## Appendix 5 Tanner Stages

### CLASSIFICATION OF SEXUAL MATURITY STATES IN GIRLS

SMR* STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

### CLASSIFICATION OF SEX MATURITY STATES IN BOYS

SMR* STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

From [Tanner JM: Growth at adolescence, ed 2, Oxford, England, 1962, Blackwell Scientific.](#)

\* SMR = sexual maturity rating.

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## Appendix 6 Epworth Sleepiness Scale for Children and Adolescents – ESS (CHAD) (Research Version)

In the last week, how likely have you been to fall asleep while doing the things that are described below (activities)? Please check the box that describes you best in the last week.

Even if you haven't done some of these things in the last week, try to imagine how they would have affected you.

It is important that you answer every question as best you can.

<p>1. Sitting and reading</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>2. Sitting and watching TV or a video</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>3. Sitting quietly in a classroom at school during the morning</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>4. Sitting and riding in a car or a bus for about half an hour</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p>	<p>5. Lying down to rest or nap in the afternoon</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>6. Sitting and talking to someone</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>7. Sitting quietly by yourself after lunch</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p> <p>8. Sitting and eating a meal</p> <p><input type="checkbox"/> Would never fall asleep</p> <p><input type="checkbox"/> Slight chance of falling asleep</p> <p><input type="checkbox"/> Moderate chance of falling asleep</p> <p><input type="checkbox"/> High chance of falling asleep</p>
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Xyrem<sup>®</sup> (sodium oxybate) oral solution  
Clinical Study Protocol: 13-005 Amendment 5

Jazz Pharmaceuticals

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**Appendix 7      SF-10<sup>™</sup> Health Survey for Children**

# SF-10™ Health Survey for Children

## INSTRUCTIONS

1. This survey asks about your child's health and well-being.
2. There are no right or wrong answers.
3. If you are unsure how to answer an item, please give the best response you can.
4. For each item, please select the response that best describes your answer by marking the appropriate box .
5. Please answer all items.

**Thank you for completing this survey.**

# SF-10™ Health Survey for Children

1. In general, would you say your child's health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems?

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
	▼	▼	▼	▼
a. Doing things that take some energy such as riding a bike or skating?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
b. Bending, lifting or stooping?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

3. During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of PHYSICAL health problems?

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

4. During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of EMOTIONAL or BEHAVIORAL problems?

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

5. During the past 4 weeks, how much bodily pain or discomfort has your child had?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

# SF-10™ Health Survey for Children

6. During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. During the past 4 weeks, how satisfied do you think your child has felt about his/her life overall?

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

8. During the past 4 weeks, how much of the time do you think your child acted bothered or upset?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. Compared to other children your child's age, in general would you say his/her behavior is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Xyrem® (sodium oxybate) oral solution  
Clinical Study Protocol: 13-005 Amendment 5

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## **Appendix 8      Columbia-Suicidality Severity Rating Scales (C-SSRS)**

- Children's Baseline/Screening [for ages under 12 years](#)
- Children's Since Last Visit [for ages under 12 years](#)
- Baseline/Screening [for ages 12 years and older](#)
- Since Last Visit [for ages 12 years and older](#)

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)

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<b>SUICIDAL IDEATION</b>			
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Lifetime	Past 6 Months
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you thought about being dead or what it would be like to be dead?</i> <i>Have you wished you were dead or wished you could go to sleep and never wake up?</i> <i>Do you ever wish you weren't alive anymore?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you thought about doing something to make yourself not alive anymore?</i> <i>Have you had any thoughts about killing yourself?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?</i> <i>This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?</i> <i>What was your plan?</i> <i>When you made this plan (or worked out these details), was any part of you thinking about actually doing it?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>			
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).  <b>Most Severe Ideation:</b> _____ <div style="display: flex; justify-content: space-between; width: 100%;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>		Most Severe	Most Severe
<b>Frequency</b> <i>How many times have you had these thoughts?</i> _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable		_____	_____

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>			<b>Lifetime</b>
<b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. <b>Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore? What did you do?</b> <b>Did you ever hurt yourself on purpose? Why did you do that?</b> Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to make yourself not alive anymore when you _____? Or did you think it was possible you could have died from _____? <b>Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent) If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____  Yes No <input type="checkbox"/> <input type="checkbox"/> Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b>  <b>Has subject engaged in Self-Injurious Behavior, intent unknown?</b>			
<b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act ( <i>if not for that, actual attempt would have occurred</i> ). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. <b>Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?</b> If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____
<b>Aborted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <b>Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?</b> If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____
<b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <b>Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?</b> If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?			Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Answer for Actual Attempts Only</b>			
	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
<b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code  _____	Enter Code  _____	Enter Code  _____
<b>Potential Lethality: Only Answer if Actual Lethality=0</b> Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).  0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code  _____	Enter Code  _____	Enter Code  _____

# **COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)**

Children's Since Last Visit

Version 6/23/10

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@nyspi.columbia.edu](mailto:posnerk@nyspi.columbia.edu)

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<b>SUICIDAL BEHAVIOR</b> (Check all that apply, so long as these are separate events; must ask about all types)	Since Last Visit
<p><b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. <b>Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?</b> <b>Did you hurt yourself on purpose? Why did you do that?</b> Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to make yourself not alive anymore when you _____? Or did you think it was possible you could have died from _____? <b>Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent) If yes, describe:</p> <p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Has subject engaged in Self-Injurious Behavior, intent unknown?</b></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. <b>Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?</b> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>
<p><b>Aborted Attempt or Self-Interrupted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <b>Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?</b> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted or self-interrupted _____</p>
<p><b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <b>Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?</b> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date: _____</p>
<p><b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p>Enter Code _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b> Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).  0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	<p>Enter Code _____</p>

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

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*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)*

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<b>SUICIDAL IDEATION</b>			
<i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>		<b>Lifetime: Time He/She Felt Most Suicidal</b>	<b>Past ___ Months</b>
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>			
<i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>			
Lifetime - <b>Most Severe Ideation:</b> _____ <i>Type # (1-5)</i> <i>Description of Ideation</i>		Most Severe	Most Severe
Past X Months - <b>Most Severe Ideation:</b> _____ <i>Type # (1-5)</i> <i>Description of Ideation</i>			
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		___	___
<b>Duration</b> <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		___	___
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts		___	___
<b>Deterrents</b> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply		___	___
<b>Reasons for Ideation</b> <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply		___	___

Version 1/14/09

<b>SUICIDAL BEHAVIOR</b> (Check all that apply, so long as these are separate events; must ask about all types)		<b>Lifetime</b>		<b>Past <u>  </u> Years</b>	
<b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. <b>Have you made a suicide attempt?</b> <b>Have you done anything to harm yourself?</b> <b>Have you done anything dangerous where you could have died?</b> What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or Did you think it was possible you could have died from _____? <b>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent) If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____		
<b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b> <input type="checkbox"/> <input type="checkbox"/>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>		
<b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. <b>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____		
<b>Aborted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <b>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____		
<b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <b>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>		
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>		
<b>Answer for Actual Attempts Only</b>		Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:	
<b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death		Enter Code  _____	Enter Code  _____	Enter Code  _____	
<b>Potential Lethality: Only Answer if Actual Lethality=0</b> Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).  0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care		Enter Code  _____	Enter Code  _____	Enter Code  _____	

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@nyspi.columbia.edu](mailto:posnerk@nyspi.columbia.edu)*

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<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<p><b>Actual Attempt:</b>                      A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.                      Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.  <b>Have you made a suicide attempt?</b>  <b>Have you done anything to harm yourself?</b>  <b>Have you done anything dangerous where you could have died?</b>  <i>What did you do?</i>                      Did you _____ as a way to end your life?                      Did you want to die (even a little) when you _____?                      Were you trying to end your life when you _____?                      Or did you think it was possible you could have died from _____?  <b>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent)                      If yes, describe:</p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts                      _____</p> <p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Interrupted Attempt:</b>                      When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).                      Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.                      Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.  <b>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</b>                      If yes, describe:</p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted                      _____</p>
<p><b>Aborted Attempt:</b>                      When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.  <b>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</b>                      If yes, describe:</p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted                      _____</p>
<p><b>Preparatory Acts or Behavior:</b>                      Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).  <b>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</b>                      If yes, describe:</p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b>                      Suicidal behavior was present during the assessment period?</p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p>Yes No  <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date:</p>
<p><b>Actual Lethality/Medical Damage:</b>                      0. No physical damage or very minor physical damage (e.g., surface scratches).                      1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).                      2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).                      3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).                      4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).                      5. Death</p>	<p>Enter Code                      _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b>                      Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).                      0 = Behavior not likely to result in injury                      1 = Behavior likely to result in injury but not likely to cause death                      2 = Behavior likely to result in death despite available medical care</p>	<p>Enter Code                      _____</p>

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**Appendix 9      Children's Depression Inventory 2<sup>nd</sup> Edition Self-  
Report Short Version (CDI 2:SR[S])**

By Maria Kovacs, Ph.D.

<b>CDI<sup>2</sup></b> <b>SELF-REPORT</b> <b>SHORT</b>	Name/ID: _____	Date of Birth: _____ / _____ / _____ <small>Year      Month      Day</small>
	Age: _____      Grade: _____	Sex:    Male    Female      Today's Date: _____ / _____ / _____ <small>Year      Month</small>

Kids sometimes have different feelings and ideas.

This form lists the feelings and ideas in groups. From each group of three sentences, pick **one** sentence that describes you best for the **past two weeks**. After you pick a sentence from the first group, go on to the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark like this  next to your answer. Put the mark in the box next to the sentence that you pick.

Here is an example of how this form works. Try it. Put a mark next to the sentence that describes you best.

**Example:**

I read books all the time.

I read books once in a while.

I never read books.

**Remember, for each group, pick out the sentence that describes you best in the PAST TWO WEEKS.**

<p><b>Item 1</b></p> <p><input type="checkbox"/> I am sad once in a while.</p> <p><input type="checkbox"/> I am sad many times.</p> <p><input type="checkbox"/> I am sad all the time.</p>	<p><b>Item 7</b></p> <p><input type="checkbox"/> I feel cranky all the time.</p> <p><input type="checkbox"/> I feel cranky many times.</p> <p><input type="checkbox"/> I am almost never cranky.</p>
<p><b>Item 2</b></p> <p><input type="checkbox"/> Nothing will ever work out for me.</p> <p><input type="checkbox"/> I am not sure if things will work out for me.</p> <p><input type="checkbox"/> Things will work out for me O.K.</p>	<p><b>Item 8</b></p> <p><input type="checkbox"/> I cannot make up my mind about things.</p> <p><input type="checkbox"/> It is hard to make up my mind about things.</p> <p><input type="checkbox"/> I make up my mind about things easily.</p>
<p><b>Item 3</b></p> <p><input type="checkbox"/> I do most things O.K.</p> <p><input type="checkbox"/> I do many things wrong.</p> <p><input type="checkbox"/> I do everything wrong.</p>	<p><b>Item 9</b></p> <p><input type="checkbox"/> I have to push myself all the time to do my schoolwork.</p> <p><input type="checkbox"/> I have to push myself many times to do my schoolwork.</p> <p><input type="checkbox"/> Doing schoolwork is not a big problem.</p>
<p><b>Item 4</b></p> <p><input type="checkbox"/> I have fun in many things.</p> <p><input type="checkbox"/> I have fun in some things.</p> <p><input type="checkbox"/> Nothing is fun at all.</p>	<p><b>Item 10</b></p> <p><input type="checkbox"/> I am tired once in a while.</p> <p><input type="checkbox"/> I am tired many days.</p> <p><input type="checkbox"/> I am tired all the time.</p>
<p><b>Item 5</b></p> <p><input type="checkbox"/> I am important to my family.</p> <p><input type="checkbox"/> I am not sure if I am important to my family.</p> <p><input type="checkbox"/> My family is better off without me.</p>	<p><b>Item 11</b></p> <p><input type="checkbox"/> Most days I do not feel like eating.</p> <p><input type="checkbox"/> Many days I do not feel like eating.</p> <p><input type="checkbox"/> I eat pretty well.</p>
<p><b>Item 6</b></p> <p><input type="checkbox"/> I hate myself.</p> <p><input type="checkbox"/> I do not like myself.</p> <p><input type="checkbox"/> I like myself.</p>	<p><b>Item 12</b></p> <p><input type="checkbox"/> I do not feel alone.</p> <p><input type="checkbox"/> I feel alone many times.</p> <p><input type="checkbox"/> I feel alone all the time.</p>



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 1-800-268-6011, 1-416-492-2627, Fax 1-416-492-3343. Internationally, +1-416-492-2627. Fax, +1-416-492-3343 or (888) 540-4484.

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**Appendix 10      Multi-dimensional Anxiety Scale for Children  
                                 (MASC-10)**

# MASC–10: Multidimensional Anxiety Scale for Children–10 Item

by John March, M.D., M.P.H.

Name: \_\_\_\_\_ Age: \_\_\_\_\_ Sex: Male Female  
(Circle one)

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ School Grade: \_\_\_\_\_  
Month Day Year

This questionnaire asks you how you have been thinking, feeling, or acting recently. For each item, please circle the number that shows how often the statement is true for you. If a sentence is true about you a lot of the time, circle 3. If it is true about you some of the time, circle 2. If it is true about you once in a while, circle 1. If a sentence is not ever true about you, circle 0. Remember, there are no right or wrong answers, just answer how you have been feeling recently.

Here are two examples to show you how to complete the questionnaire. In Example A, if you were hardly ever scared of dogs, you would circle 1, meaning that the statement is rarely true about you. In Example B, if thunderstorms sometimes upset you, you would circle 2, meaning that the statement is sometimes true about you.

	never true about me	rarely true about me	sometimes true about me	often true about me
Example A I'm scared of dogs .....	0	①	2	3
Example B Thunderstorms upset me .....	0	1	②	3

Now try these items yourself.

- |  |   |   |   |   |
|--|---|---|---|---|
| 1. The idea of going away to camp scares me .....                  | 0 | 1 | 2 | 3 |
| 2. I'm afraid that other kids will make fun of me .....            | 0 | 1 | 2 | 3 |
| 3. I try to stay near my mom or dad .....                          | 0 | 1 | 2 | 3 |
| 4. I get dizzy or faint feelings .....                             | 0 | 1 | 2 | 3 |
| 5. I feel restless and on edge .....                               | 0 | 1 | 2 | 3 |
| 6. I feel sick to my stomach .....                                 | 0 | 1 | 2 | 3 |
| 7. I get nervous if I have to perform in public .....              | 0 | 1 | 2 | 3 |
| 8. Bad weather, the dark, heights, animals, or bugs scare me ..... | 0 | 1 | 2 | 3 |
| 9. I check to make sure things are safe .....                      | 0 | 1 | 2 | 3 |
| 10. I feel shy .....   | 0 | 1 | 2 | 3 |

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## Appendix 11 Cataplexy Frequency Diary

### To be completed in the evening

Subject Number: \_\_\_\_\_

Date: \_\_\_\_\_

Please check who is completing the diary:  Parent/Guardian  Subject

Cataplexy is a sudden feeling of weakness in your legs, arms, head, or face.

It can be different for each person.

These are some examples of cataplexy:

- Falling down or feeling weak in my legs
- Feeling weak in my arms or like I couldn't move my arms
- My face doing weird things (for example: my tongue sticking out, mouth opening, eyes closing or eyes rolling)
- My head dropping or feeling like I couldn't hold my head up

Yes, I had cataplexy today

No, I did not have cataplexy today

If yes, next  
screen



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Enter the total number of times you had  
cataplexy today:

\_\_\_\_\_ time(s)

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## Appendix 12 Study Drug Dosing Diary

### To be completed in the morning

Subject Number: \_\_\_\_\_

Date: \_\_\_\_\_

Please check who is completing the diary:  Parent/Guardian  Subject

Was the first nightly dose taken?  Yes  No

Was the second nightly dose taken?  Yes  No

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## Appendix 13 Stimulant Dosing Diary

### To be completed in the evening

Subject Number: \_\_\_\_\_

Date: \_\_\_\_\_

Please check who is completing the diary:  Parent/Guardian  Subject

Did you take a stimulant today?  Yes  No

If the answer is “No”, the following item will be displayed:

Select the reason the stimulant was not taken today.

“I was supposed to take stimulant today, but I didn’t”

“I was not supposed to take stimulant today”

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## Appendix 14 School Attendance Diary

Subjects or the parent(s)/guardian(s) will record the following during the last 2 weeks of the Stable-Dose Period and during the Double-Blind Period.

Date: \_\_\_\_\_

Parent/guardian completed:

Was your child scheduled to attend school today?  Yes  No

If yes, then did your child miss school today because of narcolepsy?  Yes  No

Date: \_\_\_\_\_

Subject completed:

Were you scheduled to attend school today?  Yes  No

If yes, then did you miss school today because of narcolepsy?  Yes  No

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## **Appendix 15      Clinical Global Impression of Severity (CGIs) for Historical Narcolepsy Overall Severity Prior to any Narcolepsy Treatment**

Investigators will rate their impression of the severity of the subject's narcolepsy overall prior to any narcolepsy treatment as follows:

Considering your total clinical experience with narcolepsy subjects, how ill was the subject before he/she received any narcolepsy treatment?

- Normal; no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Severely ill
- Among the most extremely ill

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## **Appendix 16      Clinical Global Impression of Severity (CGIs) for Historical Cataplexy Severity Prior to any Narcolepsy Treatment**

Investigators will rate their impression of the severity of the subject's cataplexy prior to any narcolepsy treatment as follows:

Considering your total clinical experience with narcolepsy subjects, how ill was the subject before he/she received any narcolepsy treatment?

- Normal; no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Severely ill
- Among the most extremely ill

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## **Appendix 17      Clinical Global Impression of Severity (CGIs) for Narcolepsy Overall**

Investigators will rate their impression of the severity of the subject's narcolepsy overall as follows:

Considering your total clinical experience with narcolepsy subjects, how ill is the subject at this time?

- Normal; no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Severely ill
- Among the most extremely ill

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## **Appendix 18      Clinical Global Impression of Severity (CGIs) for Cataplexy Severity**

Investigators will rate their impression of the severity of the subject's cataplexy as follows:

Considering your total clinical experience with narcolepsy subjects, how ill is the subject at this time?

- Normal; no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Severely ill
- Among the most extremely ill

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## **Appendix 19 Patient Global Impression of Change (PGIc) for Narcolepsy Overall**

The PGIc is a 7-point scale. Subjects will be asked “How would you rate your narcolepsy since Visit 3 (the end of the Stable-Dose Period)?”

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

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## **Appendix 20      Clinical Global Impression of Change (CGIc) for Narcolepsy Overall**

Investigators will rate their impression of any change in the severity of a subject's overall condition of narcolepsy since the start of the Double-Blind Treatment Period using the CGIc rating scale (whether or not, in the Investigator's judgment, the improvement is entirely due to treatment) as follows:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

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## **Appendix 21      Clinical Global Impression of Change (CGIc) for Cataplexy Severity**

Investigators will rate their impression of any change in the severity of a subject's cataplexy since the start of the Double-Blind Treatment Period using the CGIc rating scale (whether or not, in the Investigator's judgment, the improvement is entirely due to treatment) as follows:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

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## Appendix 22 Part 2–Open-Label Continuation–Subjects Continuing Directly into Part 2 from Part 1

Events	Open-Label Continuation <sup>a</sup> Visits							Part 2 Study Termination/ Part 2 Early Termination Visit 42 (±7 days) Onsite
	Part 1 Visit 15 (±7 days)	Month 1 Visit 19	Month 2 Visit 20	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	
	Onsite	Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
		Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
		Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
(±7 days) Phone call		(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call			
Confirm informed Consent/Assent for Amendment 5	X							Maintain monthly schedule for Months 1 through 23 until the subject reaches age 18 years <sup>b</sup> or within 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first.
Physical Examination including brief neurological exam	X							
Tanner Stage Assessment	X							
Height	X			X			X	
Weight	X			X			X	
Chemistry, Hematology	X							
Urinalysis	X							
<u>Only for Girls &lt;8 years:</u> Estradiol, LH, FSH <u>Only for Boys &lt;9 years:</u> Testosterone, LH, FSH	X							
Urine Drug Screen	X						X	
Alcohol Test	X						X	
Urine Pregnancy test	X						X	

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## Appendix 22 Part 2–Open-Label Continuation–Subjects Continuing Directly into Part 2 from Part 1

Events	Open-Label Continuation <sup>a</sup> Visits							Part 2 Study Termination/ Part 2 Early Termination Visit 42 (±7 days) Onsite
	Part 1 Visit 15 (±7 days)	Month 1 Visit 19	Month 2 Visit 20	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	
	Onsite	Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
		Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
		Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
(±7 days) Phone call		(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call			
Review Study Drug Dosing Diary	X							
12-Lead ECG	X							
Vital Signs <sup>c</sup>	X			X			X	X
Review Cataplexy frequency diary	X							
ESS (CHAD)	X							
C-SSRS <sup>d</sup>	X							
Depression scale (CDI2:SR[S])	X							
Anxiety scale (MASC-10)	X							
Quality of Life (SF-10)	X							
PSG	X <sup>e</sup>							
Fasting morning blood sample: GH, IGF-1, prolactin	X <sup>e</sup>							
AE Reporting								→
Concomitant Medications	X	X	X	X	X	X	X	X
Dispense Study Drug <sup>f</sup>	X			X			X	

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## Appendix 22 Part 2–Open-Label Continuation–Subjects Continuing Directly into Part 2 from Part 1

Events	Open-Label Continuation <sup>a</sup> Visits							Part 2 Study Termination/ Part 2 Early Termination Visit 42 (±7 days) Onsite
	Part 1 Visit 15 (±7 days)	Month 1 Visit 19	Month 2 Visit 20	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	
	Onsite	Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
		Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
		Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
		(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call		
Collect trial medicine, measure and review compliance	X			X			X	

An arrow (  ) indicates that the assessment is continuous.

<sup>a</sup> Following Part 1, subjects may receive Xyrem treatment in Part 2 for up to an additional 2 years or until they reach 18 years of age or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI), whichever occurs first.

<sup>b</sup> For subjects turning 18 years of age, the Part 2 Study Termination visit must be scheduled prior to the subject's 18th birthday.

<sup>c</sup> Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after the subject has been resting for ≥5 minutes.

<sup>d</sup> Use Since Last Visit version for subjects ≥12 years of age and Children's versions for children <12 years of age.

<sup>e</sup> See [Appendix 1.2](#) for subjects on Xyrem at study entry and [Appendix 2.3](#) for Xyrem-Naïve Subjects at Study Entry.

<sup>f</sup> Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.

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## Appendix 23 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Do Not Require Titration

Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Visit 18 <sup>c,d</sup> Onsite	Open-Label Continuation <sup>a</sup> Visits						Part 2 Study Termination/ Part 2 Early Termination Visit 42 (±7 days) Onsite
			Month 1 Visit 19	Month 2 Visit 20	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	
			Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
			Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
			Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
			(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call		
Informed Consent/Assent	X								Maintain monthly schedule for Months 1 through 23 until the subject reaches age 18 years <sup>g</sup> or within 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first.
Inclusion/Exclusion Criteria <sup>e</sup>	X	X							
Update parent/guardian contact information	X								
Medical History <sup>f</sup>	X								
Physical Examination including a brief neurological exam	X								
Height	X	X <sup>h</sup>			X			X	
Weight	X	X <sup>h</sup>			X			X	
Chemistry, Hematology	X <sup>c</sup>								
Urinalysis	X <sup>c</sup>								
Urine Drug Screen	X <sup>c</sup>	X						X	

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## Appendix 23 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Do Not Require Titration

Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Visit 18 <sup>c,d</sup> Onsite	Open-Label Continuation <sup>a</sup> Visits						Part 2 Study Termination/ Part 2 Early Termination Visit 42 (±7 days) Onsite
			Month 1 Visit 19	Month 2 Visit 20	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	
			Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
			Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
			Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
			(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call		
Alcohol Test	X <sup>c</sup>	X						X	X
Serum Pregnancy test	X <sup>c</sup>								
Urine Pregnancy test		X						X	X
Vital Signs <sup>i</sup>	X	X <sup>h</sup>			X			X	X
AE reporting	—————→								
Concomitant medications	X	X <sup>h</sup>	X	X	X	X	X	X	X
Dispense Study Drug <sup>j</sup>		X			X			X	
Collect study drug and assess compliance					X			X	X

An arrow ( —————→ ) indicates that the assessment is continuous.

<sup>a</sup> Following Part 1, subjects may receive Xyrem treatment in Part 2 for up to an additional 2 years or until they reach 18 years of age or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI), whichever occurs first.

<sup>b</sup> All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Part 2 Screening Visit (Visit 17) starts when a subject is registered for Part 2 in IRT.

<sup>c</sup> Subjects who re-enroll within 2 weeks after completing Visit 15 in Part 1 of the study do not require clinical labs, urine drug screen, alcohol test, or serum pregnancy test at the Part 2 Screening visit. For these subjects, Visit 18 may occur on the same day as Visit 17.

<sup>d</sup> Visit 18 is within 2 weeks after Visit 17. If needed, additional screening time may be granted with permission of the Medical Monitor.

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- <sup>e</sup> Subjects must meet the inclusion and exclusion criteria for re-enrollment in Part 2 specified in Sections 4.2 and 4.3 of the protocol.
  - <sup>f</sup> Review the subject's previously recorded medical history and update any new medical history information. Record any new medical history that occurs after Visit 16 and prior to re-enrollment. Any new clinically significant condition with onset after the last Part 1 visit (Visit 16) until assent/consent is provided in Part 2 should be recorded as medical history.
  - <sup>g</sup> For subjects turning 18 years of age, the Part 2 Study Termination visit must be scheduled prior to the subject's 18th birthday.
  - <sup>h</sup> Assessment only completed for Visit 17 if Visit 17 and Visit 18 are conducted on the same day.
  - <sup>i</sup> Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after the subject has been resting for  $\geq 5$  minutes.
  - <sup>j</sup> Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation

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**Appendix 24 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Require Titration**

		Open-Label Continuation <sup>a</sup> Visits														
Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Part 2 Open-Label Titration Weeks T1-T10							--	--	Month 3 Visit 21	Month 4 Visit 22		Month 5 Visit 23	Month 6 Visit 24	Part 2 Study Term Part 2 Early Term Visit 42 (±7 days) Onsite
									Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28		Month 11 Visit 29	Month 12 Visit 30	
									Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34		Month 17 Visit 35	Month 18 Visit 36	
									Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40		Month 23 Visit 41	(±7 days) Onsite	
		Onsite	Phone Call +3 days						(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call			
		W T1 <sup>c,d</sup> Visit 18 Begin titration	W T2 Visit 18.1	W T3 Visit 18.2	Mon 1/ W T4 Visit 19	W T7 Visit 19.1	Mon 2/ W T8 Visit 20	W T10 Visit 20.1								
Informed Consent/Assent	X													Maintain monthly schedule for Months 1 through 23 until the subject reaches age 18 years <sup>g</sup> or within 3 months		
Inclusion/Exclusion Criteria <sup>e</sup>	X	X														
Update parent/guardian contact information	X															
Medical History <sup>f</sup>	X															

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**Appendix 24 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Require Titration**

		Open-Label Continuation <sup>a</sup> Visits												Part 2 Study Term Part 2 Early Term Visit 42 (±7 days) Onsite	
Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Part 2 Open-Label Titration Weeks T1-T10						--	--	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23			Month 6 Visit 24
								Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29			Month 12 Visit 30
								Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35			Month 18 Visit 36
								Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41			(±7 days) Onsite
	Onsite	Phone Call +3 days						(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call			
		W T1 <sup>c,d</sup> Visit 18 Begin titration	W T2 Visit 18.1	W T3 Visit 18.2	Mon 1/W T4 Visit 19	W T7 Visit 19.1	Mon 2/W T8 Visit 20	W T10 Visit 20.1							
Physical Examination including a brief neurological exam	X													after the US FDA decision on the addition of pediatric data to the Xyrem US PI, whichever occurs first.	
Height	X	X <sup>h</sup>								X			X	X	
Weight	X	X <sup>h</sup>								X			X	X	
Chemistry, Hematology	X														
Urinalysis	X														
Urine Drug Screen	X	X											X	X	

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**Appendix 24 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Require Titration**

		Open-Label Continuation <sup>a</sup> Visits													
Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Part 2 Open-Label Titration Weeks T1-T10							--	--	Month 3 Visit 21	Month 4 Visit 22		Month 5 Visit 23	Month 6 Visit 24
									Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28		Month 11 Visit 29	Month 12 Visit 30
									Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34		Month 17 Visit 35	Month 18 Visit 36
									Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40		Month 23 Visit 41	(±7 days) Onsite
		Onsite	Phone Call +3 days						(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call		
	W T1 <sup>c,d</sup> Visit 18 Begin titration	W T2 Visit 18.1	W T3 Visit 18.2	Mon 1/ W T4 Visit 19	W T7 Visit 19.1	Mon 2/ W T8 Visit 20	W T10 Visit 20.1								
Alcohol Test	X	X											X		
Serum Pregnancy test	X														
Urine Pregnancy test		X											X		
Vital Signs <sup>i</sup>	X	X <sup>h</sup>								X			X		
Determine if additional dose titration is necessary			X	X	X	X	X	X							
AE reporting															

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### Appendix 24 Part 2–Open-Label Continuation–Subjects Re-enrolling After Completing Part 1 and Require Titration

		Open-Label Continuation <sup>a</sup> Visits													
Events	Part 2 Screening Visit 17 <sup>b,c</sup> Onsite	Part 2 Open-Label Titration Weeks T1-T10							--	--	Month 3 Visit 21	Month 4 Visit 22	Month 5 Visit 23	Month 6 Visit 24	Part 2 Study Term Part 2 Early Term Visit 42 (±7 days) Onsite
									Month 7 Visit 25	Month 8 Visit 26	Month 9 Visit 27	Month 10 Visit 28	Month 11 Visit 29	Month 12 Visit 30	
									Month 13 Visit 31	Month 14 Visit 32	Month 15 Visit 33	Month 16 Visit 34	Month 17 Visit 35	Month 18 Visit 36	
									Month 19 Visit 37	Month 20 Visit 38	Month 21 Visit 39	Month 22 Visit 40	Month 23 Visit 41	(±7 days) Onsite	
		Onsite	Phone Call +3 days						(±7 days) Phone call	(±7 days) Phone call	(±7 days) Onsite	(±7 days) Phone call	(±7 days) Phone call		
	W T1 <sup>c,d</sup> Visit 18 Begin titration	W T2 Visit 18.1	W T3 Visit 18.2	Mon 1/ W T4 Visit 19	W T7 Visit 19.1	Mon 2/ W T8 Visit 20	W T10 Visit 20.1								
Concomitant medications	X	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drug <sup>j</sup>		X								X				X	
Collect study drug and assess compliance										X				X	

An arrow ( → ) indicates that the assessment is continuous.

<sup>a</sup> Following Part 1, subjects may receive Xyrem treatment in Part 2 for up to an additional 2 years or until they reach 18 years of age or until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI), whichever occurs first.

<sup>b</sup> All subjects will provide their written informed consent prior to the performance of any study-related procedures. The Part 2 Screening Visit (Visit 17) starts when a subject is registered for Part 2 in IRT.

<sup>c</sup> Subjects who re-enroll within 2 weeks after completing Visit 15 in Part 1 of the study do not require clinical labs, urine drug screen, alcohol test, or serum pregnancy test at the Part 2 Screening visit. For these subjects, Visit 18 may occur on the same day as Visit 17.

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- <sup>d</sup> Week T1 (Visit 18) Begin Titration is within 2 weeks after Visit 17. If needed, additional screening time may be granted with permission of the Medical Monitor.
- <sup>e</sup> Subjects must meet the inclusion and exclusion criteria for re-enrollment specified in Sections 4.2 and 4.3 of the protocol.
- <sup>f</sup> Review the subject's previously recorded medical history and update any new medical history information. Record any new medical history that occurs after Visit 16 and prior to re-enrollment. Any new clinically significant condition with onset after the last Part 1 visit (Visit 16) until assent/consent is provided in Part 2 should be recorded as medical history.
- <sup>g</sup> For subjects turning 18 years of age, the Part 2 Study Termination visit must be scheduled prior to the subject's 18th birthday.
- <sup>h</sup> Assessment only completed for Visit 17 if Visit 17 and Visit 18 are conducted on the same day.
- <sup>i</sup> Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after the subject has been resting for  $\geq 5$  minutes.
- <sup>j</sup> Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.

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## Appendix 25 Signatures of Agreement for Protocol

**Study Title:** A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy

**Study Number:** 13-005

**Original Protocol:** 14 April 2014

**Amendment 1:** 29 August 2014

**Amendment 2:** 1 April 2015

**Amendment 3:** 05 August 2015

**Amendment 4:** 05 April 2016

**Amendment 5:** 23 February 2017

This clinical study protocol was subject to critical review and has been approved by Jazz Pharmaceuticals. The following personnel contributed to writing and/or approving this protocol:

Signed: {Please see appended electronic signature page} Date: \_\_\_\_\_  


Signed: {Please see appended electronic signature page} Date: \_\_\_\_\_  


Signed: {Please see appended electronic signature page} Date: \_\_\_\_\_  




## Signature Manifestation

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