Statistical Analysis Plan

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[redacted]

Sponsor Name:	Jazz Pharmaceuticals
Protocol Number and Title:	13-005: 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
Protocol Version and Date:	Original Protocol: 14-April-2014 Amendment 1: 29-August-2014 Amendment 2: 01-April-2015 Amendment 3: 05-August-2015 Amendment 4: 05-April-2016 Amendment 5: 23-February-2017

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SAP Version:	4.0
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Jazz Pharmaceuticals

13-005

4.0

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Statistical Analysis Plan

Version: 4.0 **Version Date: 19-Jan-2018**

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
[redacted]	
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[redacted]	**Date (dd-Mmm-yyyy)**

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
A	Number of Apnea with onset during Total Sleep Time
ADaM	Analysis Data Model
AE	Adverse Event
AHI	Apnea + Hypopnea Index
AI	Apnea Index
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration time curve
BLQ	Below Limit of Quantification
CA	Number of Central Apnea with onset during Total Sleep Time
CDI 2:SR[S]	Children's Depression Inventory 2nd Edition Self-Report Short Version
CDISC	Clinical Data Interchange Standards Consortium
CGIc	Clinical Global Impression of Change
CHQ	Child Health Questionnaire
CI	Central Apnea Index
C_{max}	Maximum Plasma Drug Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CO_2	Carbon Dioxide
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-Blind

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Abbreviation	Description
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
DT	Dose Titration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDS	Excessive Daytime Sleepiness
ESS [CHAD]	Epworth Sleepiness Scale for Children and Adolescents
ET	Early Termination
$EtCO_2$	End tidal CO2
FDA	Food and Drug Administration
g	gram
GHB	Gamma-hydroxybutyrate
H	Number of Hypopnea with onset during Total Sleep Time
IEC	Institutional Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kg	Kilogram
MASC-10	Multidimensional Anxiety Scale for Children 10 item Anxiety Index
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	milliliter
OA	Obstructive Apnea
OHI	Obstructive Apnea + Hypopnea Index
OI	Obstructive Index
OL	Open-Label

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Abbreviation	Description
PD	Pharmacodynamics
PGIc	Patient Global Impression of Change
PHS	Physical Summary Score
PK	Pharmacokinetic
PP	Per Protocol
PR	Interval from the beginning of the P wave to the beginning of the QRS complex on ECG
PSG	Polysomnography
PSS	Psychosocial Summary Score
PT	Preferred Term
Q1	1st Quartile
Q3	3rd Quartile
QoL	Quality of Life
QT	Interval between the start of the Q wave and the end of the T wave on ECG
QTcB	QT Interval corrected (Bazett's correction)
REM	Rapid Eye Movement
REML	REM latency
RR	Interval between an R wave and the next R wave on ECG
S.I.	Standardized International
SAE	Serious Adverse Event
$SaO_2/Sp0_2$	Blood oxygen saturation
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable-Dose
SDTM	Study Data Tabulation Model
SF-10	SF-10 for Children
SOC	System Organ Class

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Abbreviation	Description
SOL	Sleep Onset latency
SOP	Standard Operating Procedure
STDEVD	Standard Deviation
$TcCO_2$	Transcutaneous CO_2
TEAE	Treatment-Emergent Adverse Events
T_{max}	Time to Maximum Plasma Drug Concentration
ULN	Upper Limit of Normal
USA	United States of America
WASO	Wake after persistent sleep
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

The purpose of this third amendment to the signed SAP, dated 19-Jan-2018, is to account for the planned analyses of the Part 2 data collected according to the Amendment 5 of the protocol document dated 23-Feb-2017. The Amendment 5 added an Open-Label (OL) Continuation Period, where subjects could continue to receive open label Xyrem. This amendment also describes additional safety analyses that were performed post-hoc for the clinical study report (CSR), dated 31-Aug-2017, which included the primary analysis of efficacy, PK, and safety data through 10-Feb-2017. These post-hoc analyses will also be performed at the end of the study; therefore they are included in this SAP as pre-planned analyses for the final CSR.

The purpose of this second amendment to the signed SAP, dated 05-Oct-2016, is to clarify that unblinding of the data will occur after the database snapshot for the primary analysis, which occurs after all randomized subjects discontinue or complete the Double-Blind (DB) period.

The purpose of the first amendment to the original, signed SAP, dated 17-Nov-2015, was to account for the changes in the study design instituted with the implementation of Amendment 4 of the protocol. Additional efficacy analyses were added to assess the robustness of study results. Supplemental safety analyses were added to further assess the safety profile.

The protocol was amended as a result of a pre-planned interim analysis which was conducted on the primary efficacy endpoint after 35 subjects completed or discontinued early from the study's double-blind treatment period. Data were reviewed by the study's independent Data and Safety Monitoring Board (DSMB), which recommended to "terminate the double-blind segment of the protocol as there are adequate data for deriving an inference of benefit in cataplexy" since a p-value <0.005 was achieved, showing a benefit in the response of cataplexy with Xyrem compared to placebo in the 35-subject data set. Given the primary efficacy endpoint has been reached based on the interim analysis, the protocol was amended to follow the DSMB recommendation to terminate the placebo treatment during the double-blind segment of the protocol to minimize the exposure of pediatric subjects to placebo. They also recommended to continue the Open-Label safety segment, and to continue enrollment of subjects in the Open-Label PK evaluation.

2.1. AMENDMENT UPDATES

To account for the Part 2 Open Label extension, the following sections in the SAP Version 4 (Amendment 3) were updated:

- Timing of the final analyses
- The statement of the primary objective was updated to match the protocol.
- The brief description section was updated to summarize the Part 1 portion as past tense and the Part 2 as future tense. All Part 1 analyses were pre-specified in the earlier amendment signed prior to the study unblinding.
- The Administration of Study Medication and the Study Procedures and Flowchart The Continued Access Analysis Population, for summaries of Part 2, was added.
- Summary of Deviations at the completion of Part 2 was added.
- The rules for summarizations of OL Continuation Period were added.
- The windowing rules for unscheduled visits in Part 2 were added.
- Rules for categorization of adverse events, concomitant procedures, and concomitant medications were provided.
- Key definition section has calculation of the change from the Start of Part 2 Visit included.
- The mapping rules for ET Visits in Part 2 were added.
- Summarizations of disposition, demographics, and baseline characteristics were added for Part 2.
- Medical / Surgical History section was updated to discuss addition terms for Part 2 subjects who were re-enrolled in Part 2 after completion of Part 1.
- Concomitant medication summarization was added for Part 2.
- Summaries and derivation of Xyrem Exposure for Part 2 and for combined Part 1 and Part 2 were added.
- Summaries and derivation of bottle weight compliance for Part 2 were added.

- Part 2 summaries of adverse events were added . Combined Part 1 and Part 2 summaries of adverse events were added.

- Modifications to the Laboratory evaluations section to provide a clarification in Part 1 and discuss collections during Part 2.

- Modifications to the Vital Signs section to discuss summarizations in Part 2.

- Modifications to the Physical Stature section to discuss summarizations in Part 2.

- Safety figures including Part 2 data will include Part 1 Day 1 baseline, Part 2 Day 1 baseline, and Part 2 visits.

For further understanding the safety profile of Xyrem, post-hoc analyses were performed and included in the CSR dated, 31-Aug-2017. These analyses will also be performed for the final CSR and are considered pre-planned. To account for these analyses, the following sections were updated:

- Summarization of Flavorant usage across the study

- The extent of Xyrem exposure was summarized by exposure days across the study at the maximum total nightly dose based on weight per protocol dosing guideline.

- Supplemental AE tables were created to concisely summarize results across part 1 and the study (Part 1 and Part 2).

- Additional summaries of adverse event by most recent mg/kg categories (<96.49, 96.49-127.59, and >127.59) were added.

- Safety figures (physical stature, CDI 2, and MASC-10) were updated to present the standard error for the mean, the number of observations available per time point, and include subgroups in the same plot.

The following are the key updates to the SAP Version 3 (Amendment 2) document.

A potential interim analysis after all randomized subjects completed the double-blind portion of the study was specified in SAP Version 2. This interim analysis is clarified as the primary analysis to be performed after all randomized subjects discontinue or complete the DB period of the study and after formal database snapshot. As the study is ongoing, the database will not be locked prior to the primary analysis. This will be considered the final analysis for the DB period of the study.

For this analysis, the lead [redacted] biostatistician and blinded programming team as well as the Jazz study team will be unblinded after the database snapshot.

As the DSMB members were unmasked during the efficacy interim analysis, the treatment groups were made available for the safety reviews. Thus language specifying masked treatment groups after the efficacy interim analysis was removed.

All deviations relevant for deriving the per protocol population will be defined prior to the database snapshot. This has been clarified as unblinding occurs after the database snapshot. Also, given that this is an ongoing study, the final list of protocol deviations will be available at database lock, which occurs at the end of the study.

Clarification of the sample code for Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference was updated to specify the "Table" option.
In the pharmacokinetic endpoint section, the collection times for the plasma sodium oxybate concentrations over an 8-hour period on two PK nights are clarified (on both nights, samples will be collected pre-dose, 0.75, 1.5, 2.5 and 4 (pre-2nd dose), 4.75, and 8 hours post first Xyrem dose on the PK night. This update is consistent with the language in section 10.1.

Summaries of the safety population by period are not performed for demographic, baseline characteristic and medical/surgical history results; therefore the analysis population section was clarified.

Details of the Bottle Weight Compliance calculation were corrected. The numerator and denominator represent the quantity taken determined by bottle and the amount to be taken based on the dosing log, respectively.

Graphical presentations of safety endpoints are updated to display the actual value across dosing periods. The interpretation of raw values is clearer compared to the change value over time.

The following are the key updates to the SAP Amendment 1 document.

- Clarifications were made to the Safety Populations to address updates from Protocol Amendment 4

- P-value for presentation of analysis of the primary endpoint has been changed to a nominally reported p-value since the analysis of this endpoint at the time of the interim analysis showed a p-value <0.005.

- A per protocol population is defined and will be used for sensitivity analysis of the primary efficacy endpoint and secondary efficacy endpoints.

- A sensitivity analysis assessing the Tier 3 endpoint of ESS will be performed, including baseline use of stimulants in the model.

- Efficacy endpoint analyses in the DB period will be performed separately for subjects randomized prior to the implementation of Amendment 4 and subjects who entered the DB Period after implementation of Amendment 4 and received Open-Label Xyrem.

- Safety endpoint analyses in the DB Period will be summarized by subjects who received Xyrem or placebo prior to Amendment 4, subjects who received Open-Label Xyrem after the implementation of Amendment 4, and by all subjects who received Xyrem.

- Additional by-week summaries of the weekly cataplexy attacks will be provided for the Stable-Dose (SD) Period and the DB Period.

- An additional calculation of compliance has been added, calculated as the ratio of expected quantity of drug taken (in mL) to the amount taken based on the (quantity dispensed - quantity returned).

- Additional figures summarizing endpoints over all periods of the study have been added.

- An interim analysis may be performed after all randomized subjects have completed the DB period.

2.2. RESPONSIBILITIES

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

[redacted] will provide an independent unblinded biostatistician who will produce masked/unblinded summaries for a Data and Safety Monitoring Board (DSMB). Contents of the materials to be produced will be defined in a DSMB charter. The methodology to be used for DSMB summaries will be defined within this SAP.

Calculation of non-compartmental pharmacokinetic (PK) parameters and statistical analysis of PK parameters will be completed by [redacted], and reviewed by Jazz's Clinical Pharmacologist. PK parameters determination will be required to be completed prior to each DSMB meeting, as the DSMB is charged with determining if adequate numbers of subjects have been recruited to adequately describe the pharmacokinetics of Xyrem in children and adolescents.

2.3. TIMINGS OF ANALYSES

The primary analysis of safety, efficacy and pharmacokinetics will be performed after all randomized subjects discontinue or complete the DB period. For these analyses, a formal database snapshot including data per a cut-off date is planned. These analyses were completed using a data cut-off date of 10-Feb-2017. The DSMB will review safety data on an ongoing basis, with the frequency of reviews defined in the DSMB charter. As well, an interim analysis was conducted after 35 randomized subjects completed or discontinued early from the DB Period as described in section 9.1.2.2.

The DSMB is responsible for an ongoing review of the PK data to determine if a sufficient number of subjects have data to adequately characterize the PK of Xyrem in children and adolescents.

A final analysis presenting the results of the Part 1 Open-Label Period and Part 2 Open-Label Continuation Period as well as combined summaries will be completed after database lock at the completion of the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVES

The primary objectives are:

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

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)

3.2. SECONDARY OBJECTIVE(S)

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

3.3. BRIEF DESCRIPTION

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 became effective, all subjects entering the Double-Blind Treatment Period received open-label Xyrem treatment. For administrative reasons, the term "Double-Blind Treatment Period" was continued to be used throughout the protocol. Following the Double-Blind Treatment Period (2 weeks), subjects enter an open-label extension period and continue to receive Xyrem treatment for up to one year in Part 1.

In addition, the PK of Xyrem was evaluated during Part 1 in a subset of subjects.

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

All subjects were screened 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]).

Eligibility screening was 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 were eligible for the study, were required to be evaluated by polysomnography (PSG) for sleep-disordered breathing during Screening Period.

Following Part 1 Screening, subjects who were Xyrem-naïve entered an Open-Label Titration Period. Xyrem therapy was initiated based on the subject's weight. These subjects were titrated on Xyrem to achieve a maximum clinical benefit in cataplexy and EDS while maintaining tolerability. Once the Investigator was satisfied that the Xyrem dose has been optimized, the subject could enter the Open-Label Stable-Dose Period. Subjects must have achieved a state of cataplexy stability (frequency and severity) with no further dose adjustment needed at the end of the Titration Period (up to 10 weeks). Prior to Amendment 4, any subject who showed no reduction in cataplexy compared with study entry was withdrawn from the study.

During Part 1, all subjects entered a Stable-Dose treatment period of 2 or 3 weeks length. The last 2 weeks of that period was the baseline data collection period for efficacy parameters. On the last night of the Stable-Dose Period, Xyrem-naïve subjects were assessed by PSG while taking Xyrem (End of Stable-Dose/Pre-Randomization PSG Night).

During Part 1, subjects were eligible to enter the Double-Blind Treatment Period if the dose of Xyrem remained 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 had occurred during the Stable-Dose Period, and the subject continued to meet eligibility criteria (prior to Amendment 4).

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Prior to Amendment 4 of the protocol being effective, subjects were 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 was continued as a double-blind treatment at the Stable-Dose taken in the prior 2 weeks
2. **Placebo**: Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

Subjects entering the Double-Blind Treatment Period, after Amendment 4 was effective, received Open-Label Xyrem treatment during this period.

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

Subjects who completed the entire 2-week Double-Blind Treatment Period were eligible to continue in the long-term, Open-Label Xyrem safety evaluation. The Open-Label Safety Period allowed subjects to continue Xyrem treatment for up to one year.

Subjects who were eligible to participate in the Open-Label Safety Period during Part 1 participated 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).

Subjects, who entered the Double-Blind Treatment Period before Amendment 4 was effective, 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 was higher, upon entering the Open-Label Safety Period.

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.

Subjects were then titrated up to their optimal dose as tolerated according to the Investigator's judgment (the maximum dose should not have exceeded the doses defined in Table 1 or the stable dose prior to study entry, whichever was higher, and should not have been greater than 9 g/night).

At certain study sites, eligible subjects additionally participated in the PK evaluation.

Prior to Amendment 4, PK assessments on PK Night 1 and PK Night 2 could occur during the Stable-Dose Period or during the Open-Label Safety Period as follows:

Eligible subjects spent two nights in the clinic for the PK evaluation (PK Nights 1 and 2).

- For subjects on Xyrem at study entry, PK Nights 1 and 2 occurred at the beginning of the Stable-Dose Period or during the Open-Label Safety Period after the subject has been retitrated and is on a stable dose of Xyrem. If a subject is participating in the PK evaluation during the Stable-Dose Period, PK Night 1 will occur at the beginning of the Stable-Dose Period and PK Night 2 will occur the next night (or within 15 days after PK Night 1).
- For Xyrem-naïve subjects, PK Nights 1 and 2 will occur during the Open-Label Safety Period when the subject has been retitrated and is on a stable dose of Xyrem.

After the implementation of Amendment 4, the PK assessments on PK night 1 and PK Night 2 could occur at any point from the Stable-Dose Period and onward, after the subject has reached a stable dose of Xyrem. Those subjects who were Xyrem Naive at entry or who were on Xyrem at Entry are eligible to participate.

For all subjects participating in the PK assessments, on PK Night 1, subjects received 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 returned to the clinic for PK Night 2 and received Xyrem at their stable, usual dose (administered as two equally divided doses, given while in bed at bedtime and 4 hours later).

Upon approval of Amendment 5, subjects who completed one year in the study (Part 1) 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).

Subjects continuing directly from Part 1 to Part 2 will initiate Part 2 at the Visit 15 of the Part 1 study. The site will initiate monthly phone contacts with these subjects starting with Visit 19 and every three month onsite contacts starting at Visit 21.

Subjects who have already completed Part 1 may re-enroll in Part 2. They initiate a screening period starting with Visit 17. The screening visit will occur within 2 weeks of the start of treatment in Part 2. If needed, additional screening time may be granted with the permission of the Medical Monitor.

For Part 2, subjects who had been off Xyrem for ≥ 1 month are required to do a Titration Period. The Titration Period in Part 2 may last up to 10 weeks. For subjects who have been off Xyrem for less than 1 month, titration may be required per the Investigator's judgment. Subjects requiring a Titration Period in Part 2 will be dispensed study drug at Visit 18, then the site has telephone calls with the subject at Visit 18.1 (Week T2 - occurs 10 days from Visit 18), Visit 18.2 (Week T3 - occurs 20 days from Visit 18), Visit 19 (Week T4/Mon 1 - occurs 30 days from Visit 18), Visit 19.1 (Week T7 - occurs 45 days from visit 18), Visit 20 (Week T8/Mon 2 - occurs 60 days from visit 18), and Visit 20.1 (Week T10 - occurs 75 days from visit 18). Then these subjects continue with Visits 21 – Visit 42, where onsite visits are held every three months. Visit 21 is the first scheduled onsite visit after the Titration Period.

Subjects who are re-enrolling in Part 2 and do not require Titration are dispensed study drug at Visit 18. The sites initiate monthly phone contacts with these subjects starting with Visit 19 and an onsite visit every 3 months starting at Visit 21.

3.4. SUBJECT SELECTION

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.

3.4.1. Inclusion Criteria

The inclusion criteria for the study are described completely in section 4.2 of the protocol.

3.4.2. Exclusion Criteria

The exclusion criteria for the study are described completely in section 4.3 of the protocol.

3.5. 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 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.

3.6. TREATMENT ASSIGNMENT & BLINDING

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 biostatistician [redacted] specified a dynamic randomization algorithm to assign treatments for the DB Period of the trial. The randomization balanced 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 (USA and ex-USA). The age entered by the site at the time of the randomization call is used for the treatment balancing. If emergency unblinding is required, the DB treatment assignment will be provided to the Investigator by the IWRS.

The lead [redacted] biostatistician and the blinded programming team remained blinded throughout the study conduct until all randomized subjects discontinued or completed the double-blind period and the formal database snapshot was performed. As well, the Jazz study team, with the exception of the Jazz clinical trial material supply group, remained blinded until the formal database snapshot.

The unblinded [redacted] SDTM programmer and unblinded [redacted] biostatistician received the randomization lists from the Bracket biostatistician for incorporation into the summaries presented to the DSMB, for their periodic safety reviews and interim analysis. Meetings are scheduled according to the DSMB charter. See SAP section 7.1 for details of display of treatment groups for the DSMB summaries.

For DSMB meetings, the unblinded [redacted] SDTM programmer and unblinded [redacted] biostatistician will provide analyses with masked treatment groups for DSMB members. The DSMB requested and was unblinded to the 35 randomized subjects according to the DSMB charter for the interim review of the primary efficacy endpoint for superiority, and futility.

3.7. ADMINISTRATION OF STUDY MEDICATION

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 SD Period.

Xyrem-naïve subjects entering Part 1 and subjects re-enrolling in Part 2 who have been off Xyrem for ≥ 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 of Section 3.1.2 of the protocol document. Once the Investigator is satisfied that the

Xyrem dose has been optimized, the subject may enter the 2-week SD Period if in Part 1 of the study or continue the Open-Label Continuation Period if in Part 2.

Prior to Amendment 4 becoming effective, at the end of the SD Period subjects were randomized 1:1 to receive either Xyrem or Xyrem placebo during the DB Period as follows:

- Xyrem: Active Xyrem will be continued as a DB 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 becomes effective will receive Open-Label Xyrem treatment during this period.

Prior to Amendment 4 becoming effective, upon entering the OL Period of Part 1, all subjects were started at a dose no higher than half the Xyrem dose they received at the end of the SD Period or the initiation dose defined in Table 1 of the protocol (in Section 3.1.2), whichever is higher. Subjects were then 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 of the protocol (in Section 3.1.2) or the stable dose prior to study entry, whichever is higher, and should not be greater than 9 g/night). Subjects took two equally divided doses or two unequally divided doses with the exception of PK nights, if applicable. Xyrem dose titration was allowed at no more than 1.5 g/night. Only doses that match the printed gradations (lines) on the dosing syringe were permitted.

After the Protocol Amendment 4 became effective during the Open-Label Period of Part 1 or 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. Subjects can continue the Open-Label Xyrem treatment at the appropriate dose as deemed by the investigator. 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.

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 ≥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. 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 (or of flavored diluent if requested and available; however, no flavored diluent will be provided on PSG and/or PK nights). 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.

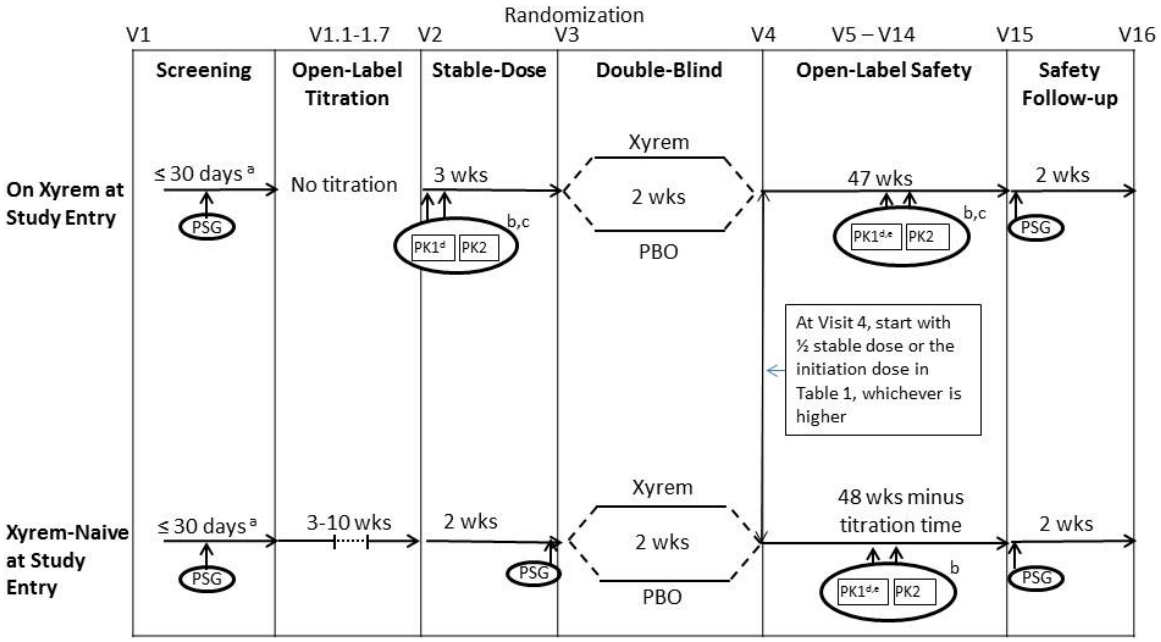
The actual time of dosing for each dose administered on PSG and PK nights will be recorded.

3.8. STUDY PROCEDURES AND FLOWCHART

The study flowchart below is reproduced from the study schema contained in Figure 1 of the protocol. This applies to subjects who entered prior to Amendment 4 becoming effective.

[redacted]

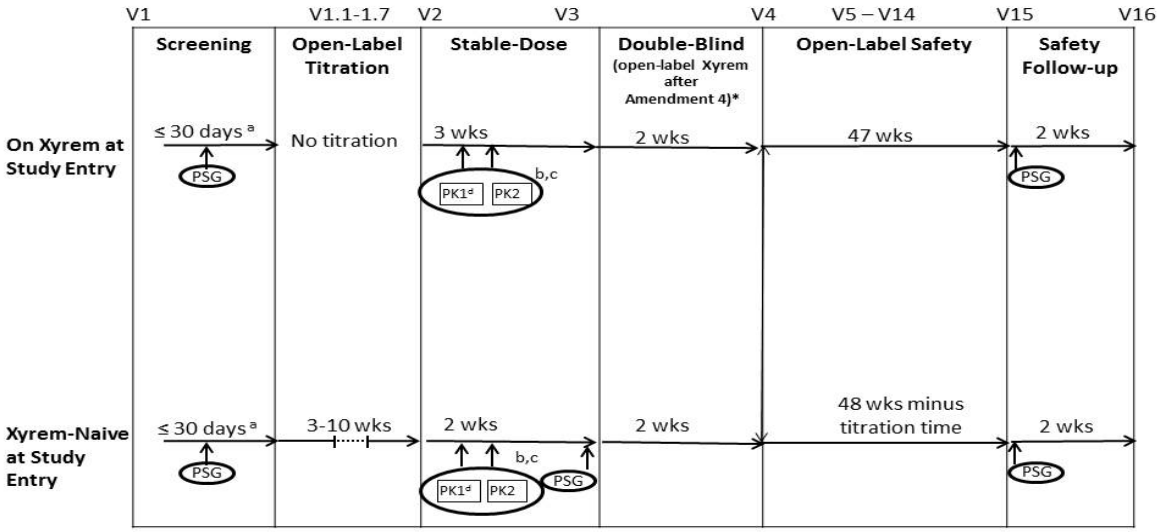
Statistical Analysis Plan



[a] Up to 30 days. If needed, additional time may be granted with permission of the Medical Monitor.
[b] PK Nights 1 and 2 are only for the subset of subjects who have provided assent/consent to participate in the PK evaluation.
[c] Either in Stable-Dose or Open-Label Safety Period.
[d] ½ of usual nightly dose. Doses must match the printed gradations (lines) on the dosing syringe. See Section 3.1.7.
[e] Once the subject is titrated and on a stable dose of Xyrem.
PBO = placebo; PSG = polysomnography; V = visit; wks = weeks

Statistical Analysis Plan

The study flowchart below is reproduced from the study schema contained in Figure 2 of the protocol. This applies to subjects who enter after Amendment 4 became effective.



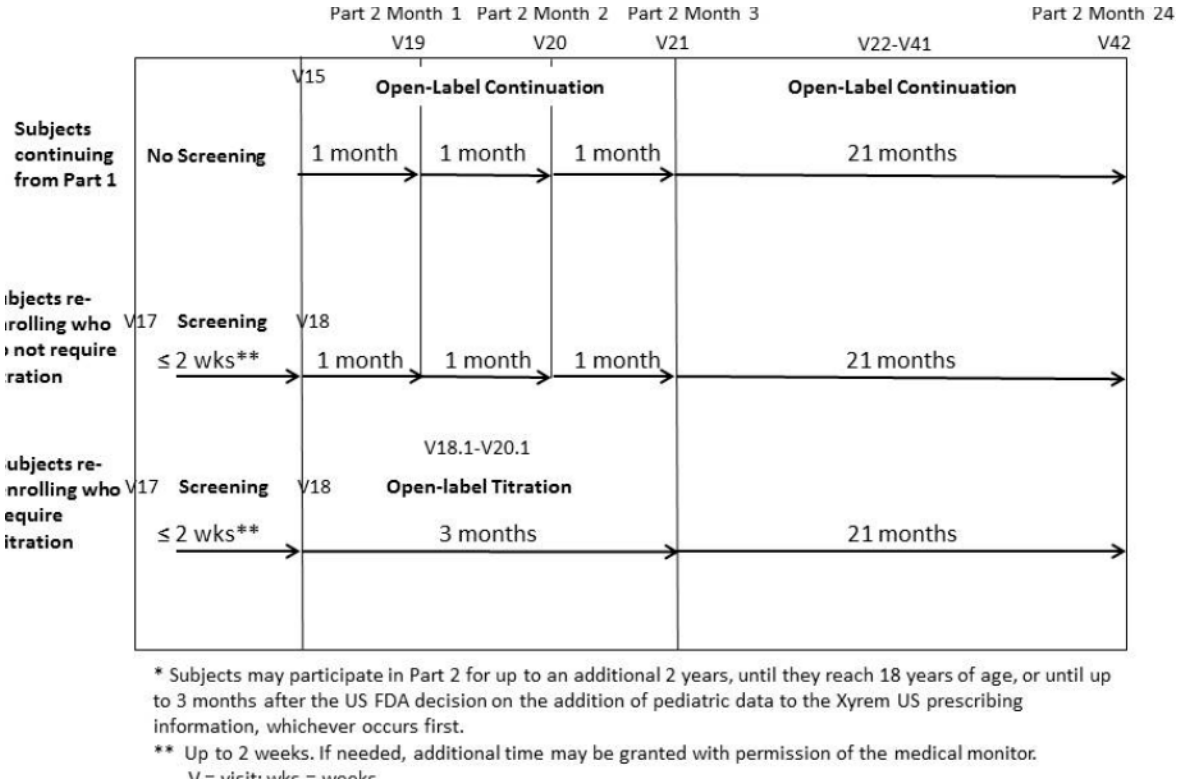
*Subjects entering the Double-Blind Period after Amendment 4 becomes effective will receive open-label Xyrem during this period.
[a] Up to 30 days. If needed, additional time may be granted with permission of the Medical Monitor.
[b] PK Nights 1 and 2 are only for the subset of subjects who have provided assent/consent to participate in the PK evaluation.
[c] Conduct PK procedures at any time from Stable-Dose Period on after the subject has reached a stable dose of Xyrem.
[d] ½ of usual nightly dose. Doses must match the printed gradations (lines) on the dosing syringe. See Section 3.1.7.
PSG = polysomnography; V = visit; wks = weeks

The schedule of evaluations to be performed at each visit in Part 1 is contained in Appendices 1 and 2 of the protocol.

- Appendix 1.1 Part 1 Screening, Stable-Dose Period, Double-Blind Treatment Period, Open-Label Treatment Period – Subjects on Xyrem at Study Entry
- Appendix 1.2 PSG Night Procedures – Subjects on Xyrem at Study Entry
- Appendix 2.1 Part1 Screening, Open-Label Titration Period, Stable-Dose Period, Double-Blind treatment Period– Xyrem-Naïve Subjects at Study Entry
- Appendix 2.2 Part1 Open-Label Safety Period–Xyrem-Naïve Subjects at Study Entry
- Appendix 2.3 PSG Night Procedures–Xyrem-Naïve Subjects at Study Entry.

- Appendix 3 PK Evaluation Procedures–Subjects Participating in the PK Evaluation

- The study flowchart below is reproduced from the study schema contained in Figure 3 of the protocol. This applies to the Part 2 period.



* 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

The schedule of evaluations to be performed at each visit in Part 2 is contained in Appendices 22, 23, and 24 of the protocol.

- Appendix 22 Part 2-Open-Label Continuation-Subjects Continuing Directly into Part2 from Part 1

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

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

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is:

- Change in the weekly number of cataplexy attacks

4.2. SECONDARY EFFICACY ENDPOINTS

4.2.1. Key Secondary Efficacy Endpoints

The two key secondary efficacy endpoints are:

- Clinical Global Impression of Change (CGIc) for cataplexy severity
- Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD]) score

4.2.2. Other Secondary Efficacy Endpoints

The other two secondary efficacy endpoints are:

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

4.3. EXPLORATORY EFFICACY ENDPOINTS

The two exploratory efficacy endpoints are:

- Change in weekly school attendance (if enrollment overlaps with school attendance period)
- PGIc for narcolepsy overall

4.4. PHARMACOKINETIC ENDPOINTS

Pharmacokinetic endpoints will include:

- Plasma sodium oxybate concentrations over an 8-hour period on two PK nights (on both nights, samples will be collected pre-dose, 0.75, 1.5, 2.5 and 4 (pre-2nd dose), 4.75, and 8 hours post first Xyrem dose on the PK night*)*

- Area under the plasma concentration time curve over the first 4-hour post-dosing interval (AUC_{0-4})
- Maximum plasma drug concentration (C_{max}) over the first 4-hour post-dosing interval
- $AUC_{0-infinity}$ using samples collected over the first 4-hour post dosing interval
- $T_{1/2}$ (Half-life) determined using samples over the first 4-hour post dosing interval
- Time to maximum drug concentration (Tmax) over the first 4-hour post-dosing
- Ratio of AUC_{0-4} on PK Night 2 to AUC_{0-4} on PK Night 1
- Ratio of C_{max} on PK Night 2 to C_{max} on PK Night 1

4.5. SAFETY ENDPOINTS

Safety will be assessed at time points specified in the schedule of events, as well as throughout the study. Safety endpoints will evaluate the safety and tolerability as determined by the occurrence of and/or changes in:

- Subject Incidence of Adverse events (AE)
- Vital Signs
- Physical examinations (including weight and height)
- 12-lead Electrocardiogram (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

4.6. OTHER SAFETY EXPLORATORY ENDPOINTS

Other endpoints will include:

CO_2 ($EtCO_2$ or $TcCO_2$)

5. STATISTICAL HYPOTHESES FOR TRIAL OBJECTIVES

The primary hypothesis, corresponding to the primary efficacy variable (weekly number of cataplexy attacks), is the following:

- Xyrem is superior to Placebo as measured by the change in the 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 statistical null hypothesis is that for the weekly number of cataplexy attacks endpoint, the rank based mean change is the same for the Xyrem treatment group and the Placebo treatment group.

In addition to the primary hypothesis, the key secondary hypotheses are:

- Xyrem is superior to Placebo as measured by CGIc for cataplexy severity at the end of the Double-Blind Treatment Period.

  The statistical null hypothesis is that for the CGIc cataplexy severity, the mean value for the Xyrem group is equal to the mean value for the Placebo treatment group.

- Xyrem is superior to Placebo as measured by the change in the ESS (CHAD) from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period.

  The statistical null hypothesis is that for the ESS (CHAD), the rank based mean change is the same for the Xyrem treatment group and the Placebo treatment group.

In addition to the key secondary hypotheses, the other secondary hypotheses are:

- Xyrem is superior to Placebo as measured by CGIc for narcolepsy overall at the end of the Double-Blind Treatment Period.

  The statistical null hypothesis is that for the CGIc narcolepsy overall, the mean value for the Xyrem group is equal to the mean value for the Placebo treatment group.

- Xyrem is superior to Placebo as measured by the change in the SF-10 Physical Health Score from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period.

The statistical null hypothesis is that for the SF-10 Physical Score, the rank based mean change is the same for the Xyrem treatment group and the Placebo treatment group.

- Xyrem is superior to Placebo as measured by the change in the SF-10 Psychosocial Score from the end of the Stable-Dose Period to the end of the Double-Blind Treatment Period.

  The statistical null hypothesis is that the rank based mean change is the same for the Xyrem treatment group and the Placebo treatment group.

6. ANALYSIS POPULATIONS

6.1. SAFETY POPULATION

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. An overall Safety Population based on subjects who took study drug (regardless of period) is also used to summarize safety data across all periods. The Safety 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 within the different study periods. Analyses will include the Safety Populations as detailed below.

The following subsets of the Safety Population will be used for disposition, concomitant medications, treatment compliance, and treatment exposure summaries in Part 1:

- Safety Population who had Study Drug Dispensed in the DT Period
- Safety Population who had Study Drug Dispensed in the SD Period
- Safety Population who had Study Drug Dispensed in the DB Treatment Period
- Safety Population who had Study Drug Dispensed in the OL Period

The following subsets of the Safety Population will be used for descriptive summaries of efficacy parameters and all safety parameters including AEs, labs, vitals, ECGs, physical measures, CDI-2, MASC-10, and CSSR-S in Part 1:

- Safety Population who took Study Drug in the DT Period
- Safety Population who took Study Drug in the SD Period
- Safety Population who took Study Drug in the DB Treatment Period
- Safety Population who took Study Drug in the OL Period

For subjects included in the Safety Population for the DB Treatment Period, summaries will be provided by the randomized treatment groups (subjects randomized to Placebo and Xyrem) and by Open-label Xyrem (subjects entering the DB period after Amendment 4).

For subjects on Xyrem at study entry who have their usual dosage of Xyrem dispensed on the PSG night at the screening assessment, administration of dose on the screening PSG night will not be considered for inclusion in the Safety Population nor be considered the first dose date.

6.2. RANDOMIZED POPULATION

The Randomized Population will consist of all subjects who are randomized to either Xyrem or Xyrem Placebo for the Double-Blind Treatment Period. This population will be used to summarize demographics and baseline characteristics.

6.3. PK HALF-DOSE POPULATION

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.

6.4. PK FULL-DOSE POPULATION

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 if this population is different from the PK completer population.

6.5. PK COMPLETER POPULATION

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.

6.6. EFFICACY POPULATION

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.

This population will include subjects who were randomized to either blinded Placebo or blinded Xyrem in the DB Period (prior to Amendment 4 being effective).

6.7. PER PROTOCOL POPULATION

The Per Protocol (PP) Population will consist of subjects from the Efficacy Population where subjects with major deviations will be assessed, flagged and excluded from this analysis population. All deviations will be reviewed and assessed prior to the data snapshot. The final list of protocol deviations will be determined and approved prior to data base lock at the end of the study.

This population will be used for sensitivity analyses of the primary and secondary efficacy endpoints during the DB period if it is found that the population is different from the efficacy population.

6.8. CONTINUED ACCESS POPULATION

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

In this SAP and in the table shells and listings, the Continued Access Population is synonymous with the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period.

6.9. PROTOCOL DEVIATIONS

Deviations from protocol will be maintained by the INC clinical team. Subjects with major deviations to be excluded from the PP population will be identified prior to database snapshot. Upon unblinding, deviations between randomized treatment assignment and actual treatment received during the DB Period will be documented and displayed in a listing. Subjects with deviations between randomized treatment assignment and actual treatment will be excluded from the PP population. A listing of deviations will be summarized using the safety population and deviations that led to exclusion from the PP population will be flagged.

For the final analysis of Part 2 data, a summary table of types of deviation and severity of the deviations (major vs. minor) will be completed using the Safety Population. The analysis will be done by Age Group, Xyrem Status at Entry, and overall.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1. GENERAL METHODS

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3 or higher.

Unless otherwise specified, summarizations will be presented separately for each period (i.e. DT Period, SD Period, DB Period, OL Period, and Part 2 OL Continuation Period) as specified below.

General Rules for Summarizations in the DT Period

Unless otherwise specified, these are the general rules for summarizations in the DT Period.

For Xyrem Naïve subjects at study entry, the visits Visit 1.1, Visit 1.2, Visit 1.3, Visit 1.4, Visit 1.5, Visit 1.6, and Visit 1.7, Visit 2 (End of Titration/Begin Stable-Dose), and Early Termination (ET) visits that occurred in the DT Period will be included in the summaries for this period.

Columns of presentation for this period will include the Age Group 7-11, Age Group 12-17, and Total.

General Rules for Summarizations in the SD Period

Unless otherwise specified, these are the general rules for summarizations in the SD Period.

Baseline values, Visit 3 (End of Stable Dose/Begin Double-Blind Period), and ET visits that occurred in the SD Period will be included in the summaries for this period.

Summarizations of the SD Period will display columns for Age Group 7-11, Age Group 12-17, Xyrem Naïve at Study Entry, On Xyrem at Study Entry, and Total.

General Rules for Summarizations in the DB Period

Efficacy analyses of DB Period data will be provided separately as follows:

- For testing of the efficacy endpoints, subjects in the Efficacy population who were randomized (Placebo or Xyrem) prior to the implementation of Amendment 4 will be assessed according to their randomized treatment group

- Columns for the randomized treatment assignment of Xyrem, Placebo and Total will be displayed
- Analyses by subgroup will be provided separately for each subgroup

- For all other applicable summaries using the Safety Population who took Study Drug in the DB Treatment Period
  - Columns for Randomized to Placebo, Randomized to Xyrem, Open-Label Xyrem, and All Xyrem will be displayed
  - Analyses by subgroup will be provided separately for each subgroup

Unless otherwise specified, these are the general rules for summarizations in the DB Period.

Visit 4 (End of Double-Blind Treatment/Begin Open-Label Safety), and ET visits that occurred in the DB Period will be included in the summaries for this period. Efficacy analyses will include the efficacy baseline value where applicable. For safety endpoints where a value is scheduled to be collected at Visit 3 (End of Stable Dose/Begin Double-Blind Period), the Visit 3 results and changes from Visit 3 will also be summarized.

The randomized treatment assignment will be used for all efficacy analyses as applicable. Actual treatment received will be used for study drug exposure and safety analyses.

Actual treatment received will be determined by comparing the dosing kit numbers assigned by the IWRS during the DB Period with the contents of those kits. Subjects who are given kits during the DB period, all containing Placebo, will be analysed as receiving Placebo. Subjects who are given at least one kit containing active Xyrem during the DB Period will be considered to have received Xyrem during the period. If any deviations between randomized treatment assignment and assigned treatment assignment occur, they will be presented in a listing.

For the DSMB summaries, the treatment groups will be masked with columns labelled as Treatment A and Treatment B, OL Xyrem, All Xyrem, and Total. The unblinded [redacted] biostatistician decides the correspondence of Treatment A and Treatment B to Placebo and Xyrem prior to the first DSMB meeting. This correspondence will be used at all successive DSMB meetings throughout the study conduct. At the time of the interim analysis, the treatment correspondence was requested by the DSMB, and then revealed.

General Rules for Summarizations in the OL Period

Unless otherwise specified, these are the general rules for summarizations in the OL Period.

Baseline value, Visit 4 (End of Double-Blind Treatment Period/Beginning of Open-Label Safety Period), Visit 5 – Visit 15 values, and ET visits that occurred in the OL Period will be included in the summaries for this period. Changes from baseline and change from end of DB Period will also be summarized.

Summarizations of measurements in the OL Period will be presented by the Age Group, Xyrem Status at Study Entry, and Total.

For the efficacy endpoints Weekly Cataplexy Attacks, ESS(CHAD), SF-10 Physical Summary Score, and SF-10 Psychosocial Summary Score, summarizations for the OL Period will also be done by the treatment received during the DB Period (Xyrem vs. Placebo).

General Rules for Summarizations for the Safety Follow-Up Assessment

Assessments made at the Safety Follow-Up Assessment in Part 1 will be listed, but otherwise will not be used in any statistical summarization unless otherwise noted.

General Rules for Summarizations in the Part 2 OL Continuation Period

Unless specified, these are the rules for summarizations of the Part 2 OL Continuation Period. Summarizations based on the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period will be based on the Age Group at first dispense in Part 1. Columns will be presented as: Age 7-11, Age 12-17, and Total.

Summarizations of combined Part 1 and Part 2 data for exposure and adverse events will be completed using the Safety Population who Took Study Drug. These summaries will be provided by the Age Group at Entry into Part 1, Xyrem Status at Study Entry, and Total.

Presentation of sample statistics

Continuous variables will be summarized using descriptive statistics including number of observations (n), mean, standard deviation (STDEV) or standard error, median, 1st quartile (Q1), 3rd quartile (Q3), minimum and maximum. Categorical variables will be summarized using the number of observations (n) and percentage of observations.

Listings

Except for PK listings and analysis population exclusion listings, all other listings will be provided using the safety population. PK listings will be presented using the PK Half-Dose Population. In general, subject data listings will present data sorted in order of Xyrem Status at Study Entry, randomized treatment (Placebo, Xyrem, OL Xyrem, or not

randomized), country, subject identifier, period of collection, visit number, date and study day of collection. Some listings, where Part 2 data is shown, will indicate that a subject entered Part 2 and the type of Part 2 subject (entered directly, re-enrolled and required titration, re-enrolled and did not require titration).

Summarization of Scheduled and Unscheduled Visits

Scheduled visits will be analysed according to their nominal label.

Unscheduled visits in Part 1 and Part 2 will be considered for analysis according to the visit number of the immediately preceding scheduled visit number within the study period. If an unscheduled visit occurs in a period where the subject has had no scheduled assessments, the unscheduled visit will be mapped according to the windows defined for the Early Termination (ET) visits.

Summarization and Mapping of ET Visits

Early termination visits will be analysed separately within the period that the termination occurred.

Early termination visits will also be mapped into a scheduled visit for summarization, according to the period in which the termination occurred and according to the rules below. An assessment at early termination can be mapped to a visit where the assessment was not scheduled to be collected. In case assessments are not scheduled to be collected within a period, early termination results will be listed.

Early termination assessments occurring in the DT Period will be mapped to a visit based on the calculated study day of the assessment. See Section 7.4 for the windows for the visits.

Early termination assessments in the SD Period will be summarized as End of Stable Dose, as there is only one scheduled SD Period visit.

Early termination assessments in the DB Period will be summarized as Double-Blind Treatment Period, as there is only one scheduled DB Period visit.

Early termination assessments in the OL Period will be mapped to a visit based on the calculated study day of the assessment. See Section 7.4 for the windows for the visits.

Early termination assessments in the Part 2 OL Continuation Period will be mapped to a visit based on the calculated study day of the assessment relative to the first dose date in Part 2. See section 7.4 for the windows for the visits.

Multiple Assessments within a Visit

For Part 1, if multiple assessments have occurred within the same analysis visit, either due to unscheduled assessments or early termination mapping, then the first recorded value will be used for the by-visit summary, unless specified otherwise.

For Part 2, if multiple assessments have occurred within the same analysis visit, then the first recorded value will be used in the by-visit summary.

For shift tables where abnormal values are presented, the worst value (abnormal values are worse than normal) within the visit will be used in the summary.

Categorization of AEs, Concomitant Procedures, and Concomitant Medications into Periods

AEs, concomitant procedures, and concomitant medications will be categorized as occurring in periods if the AE Onset, Procedure Date, or period of use of the concomitant medication overlaps the periods defined below:

Xyrem Status at Study Entry	Period	Starting Day (inclusive)	Ending Day (inclusive)
Xyrem Naïve Subjects and on Xyrem at Study Entry Subjects	Screening	No Lower Bound	Day before Study Day 1
Xyrem Naïve Subjects	DT Period	1st Day of Intake after Visit 1.1	Day prior to first evening intake after Visit 2
Xyrem Naïve Subjects and on Xyrem at Study Entry Subjects	SD Period	1st Day of Intake after Visit 2	Day prior to first evening intake after Visit 3
	DB Period	1st Day of Intake after Visit 3	Day prior to first evening intake after Visit 4

Xyrem Status at Study Entry	Period	Starting Day (inclusive)	Ending Day (inclusive)
	OL Period	1st Day of Intake after Visit 4	Last date in the Period for Concomitant Medications and Concomitant Procedures; 30 days after last dose of study drug, inclusive, for Adverse Events. (See notes *, **).
Part 2 Subjects	OL Continuation Period	1st Day of Intake in Part 2	30 days after last dose of study drug in Part 2, inclusive, for Adverse Events. (See notes *, **).

AEs, concomitant procedures, and concomitant medications that occur after the last period in which the subject had study drug dispensed, will be allocated to the subject's final dispense period in which study medication was taken.

* For subjects who did not continue into Part 2, Concomitant medications and Concomitant procedures with start date strictly after the last date in the study period will be allocated to the post-treatment follow-up period. They will be shown in listings only, and not included in the summary tables. For subjects who entered Part 2, concomitant medications eCRF with start date strictly after the last date in the OL study period, but strictly prior the first dose date in Part 2 will be summarized as Part 2 prior medication.
** For subjects who did not continue into Part 2, adverse events with onset more than 30 days after the last dose of study drug in Part 1 will be allocated to the post-treatment follow-up period. They will be shown in listings only, and not included in the summary tables.

Handling of incomplete dates for AEs and concomitant medications will be discussed specifically in the Section 7.3.

7.2. KEY DEFINITIONS

Dispensation of Study Drug

Dispensation of study drug in the periods will be based on the eCRF forms entitled "Study Drug Administration Titration Dosing", "Study Drug Administration Stable Dosing" (which also contains the dispensation of DB Period data when the visit number is 3), "Study Drug Administration Open Label Safety Dosing", and Study Drug Administration – Part 2. The earliest assignment date will be called the first study drug dispensation date.

First Dose Intake in Part 1

Dose intake will be determined using the two eCRF pages entitled "Study Drug First Taken" and "Study Drug Last Taken", and the morning diary entries to the questions "Was the first nightly dose taken?" and "Was the second nightly dose taken?" As these diary questions are answered in the morning and the dosing should occur in the evening prior to going to bed, if the response to either question is Yes, then the date of intake will be considered to be 1 calendar date prior to the diary date. The earliest date of intake from the "Study Drug First Taken" eCRF page and the morning diary entries will be the date of first dose intake.

A subject will be considered to have taken a study dose in the study, if they have either the "Study Drug First Taken" in the DT Period (for Xyrem Naïve) or SD Period (for those on Xyrem at Study Entry) or if they have at least one morning diary entry where the answer to either dose taken question is Yes after the first dispense in the treatment period.

First Dose Intake in Part 2

The first dose intake in Part 2 will be based on the eCRF entry on the page titled "Study Drug First Taken" entered for Part 2 subjects.

Study Day 1 in Part 1

Study day 1 is the first study drug dispensation date. For Xyrem Naïve subjects, this is the first study drug assignment date record on the Study Drug Administration Titration Dosing page. For subjects on Xyrem at Study Entry, this is the dose assignment date on the Study Drug Administration Stable Dosing Page for Visit 2.

Last Dose Date in Part 1

If the investigator has completed the eCRF entitled "Study Drug Last Taken", then the last dose date will be the date entered on this eCRF.
Otherwise, the last dose date will be the calendar day of the last morning diary where at least one response to the dose taken questions is Yes.

Study Day

For Part 1, study day will be calculated from the date of Study Day 1. If the assessment date is on or after Study Day 1 date, then Study Day = date of assessment – Study Day 1 date + 1. If the assessment date is prior to Study Day 1, then Study Day = assessment date – Study Day 1 date. In this way, the day prior to Study Day 1 is noted as study day -1. There will be no Study Day 0.

For Part 2, a second study day will be calculated using the date of first dose in Part 2. If the assessment date is on or after the first dose in Part 2, then the second study day = date of assessment – first dose date + 1.

Duration of Dosing in Periods

Durations will be measured in days counting from the last date of dosing during the period minus the first date of dosing during the period + 1. Xyrem Naïve subjects at study entry will have durations for up to 4 treatment periods (DT, SD, DB, and OL) in Part 1. Subjects on Xyrem at study entry will have durations for up to 3 treatment periods (SD, DB, and OL) in Part 1.
For the Part 2 OL Continuation period, the duration of dosing = date of last dose in Part 2 – date of first dose in Part 2 + 1.

Total Duration of Dosing

The total duration of dosing in Part 1 will be calculated as Last Dose Date – First Dose Intake Date + 1.

For combined Part 1 and Part 2 Duration of Dosing, the Total Duration of dosing will be the sum of the durations of dosing in Part 1 and Part 2. If the last dose date in Part 1 is the same as the first dose date in Part 2, then the sum will have one day subtracted.

Total Duration of Xyrem Usage

For subjects who received Xyrem or OL Xyrem during the DB Period, the duration of Xyrem usage will be the same as the Total Duration of Dosing. For subjects who received Placebo during the DB Period, Total Duration of Xyrem Usage will equal the Total Duration of Dosing minus Duration of Treatment during the DB Period. A similar adjustment will be made for the combined Part 1 and Part 2 Duration of Xyrem Usage.

Cumulative Dosage of Study Drug Used in a Period

During each period in Part 1, the cumulative dosage of study drug (in g) will be determined utilizing the study medication dosage level assigned by the investigator on

the dosing log (in g/night) and the daily diary entries. On a morning diary where subjects indicated they did not take one of the previous night's doses, the total dosage for that night will be determined using the relative typical 1st nightly dose amount and 2nd nightly dosage amount. On a morning diary where the subjects indicated they took neither of the doses, the total dosage for that night will be 0. Missing diary entries will count as 0 toward the cumulative dosage used. For subjects who actually receive Placebo during the DB period, their cumulative Xyrem dosage during the DB period will be equal to 0.

Because the daily diary entries are not collected in Part 2, an additional cumulative Xyrem dosage will be calculated based on dosing log only. This cumulative Xyrem dosage amount will be used only for the presentation of results in Part 2 and the combined Part 1 and Part 2 analyses. For each row on the dosing log, the dosage received will be calculated as the assigned dosage level (g/night) multiplied by the duration of time on that dosage, up to and including the last dose date in the period. The cumulative dose will be determined by adding each dosing log row's dosage received value. For subjects who received Placebo during the DB period, their cumulative Xyrem dosage during the DB period will be set equal to 0.

Average Dosage of Xyrem Used in a Period

During the Part 1 OL period, the average dosage of Xyrem used during the period will be calculated as the cumulative dosage received (in g) (based on the diary entries and dosing log) and dividing by the duration of dosing in the period (in days).

Calculation of Xyrem Dosage in mg/kg/night

The dosage in mg/kg/night is calculated using the total nightly dosage assigned by the investigator (measured in g/night; called SDDOSE in the formula below) and the body weight (kg) (called WEIGHT in the formula below).

DOSELEV = (SDDOSE x 1000) / WEIGHT.

For the DT period, the weight collected closest up to the date of the Visit 1.1 will be used. For the SD and DB period, the weight collected closest to the date of the Visit 2 will be used. For the OL period in Part 1, the dosage at last dose will be determined using the weight closest to the last dose. For PK nights and PSG nights, the weight collected closest to the collection night will be used. For visits in the Part 2 OL Continuation Period, the weight collected closest to the date of dose adjustment will be used.

Xyrem dosage in mg/kg/night will be categorized as follows:

50-100 mg/kg/night
>100 – 150 mg/kg/night
> 150 – 200 mg/kg/night
> 200 mg/kg/night

Baseline Values

For the cataplexy frequency endpoints and school attendance endpoints (i.e. endpoints calculated from daily diary entries), the baseline value will be calculated based on the diaries during the last 2 weeks of the SD Period.

For the other efficacy endpoints: ESS (CHAD), and SF-10 scores, the baseline value will be the Visit 3 assessment (End of Stable Dose/Begin Double-Blind Period).

For the safety endpoints, the baseline assessment will be the last non-missing value collected on or prior to Study Day 1.

Change from Baseline and Percentage Change from Baseline Values

Change from baseline will be calculated as Observed Value – Baseline Value.

If the Baseline value is not-missing, and not 0, then percentage change will be calculated as: (Change from Baseline / Baseline Value) * 100%.

Change from Visit 3 (End of Stable Dose/Begin Double-Blind Period), and Percentage Change from Visit 3

For the following safety endpoints in the DB Period: Vital Signs, Physical Stature, CDI 2:SR[S], and MASC-10, the change from Visit 3 will be calculated as Observed Value in DB – Visit 3 value, where the Visit 3 value will be the collected value at Visit 3 and prior to the first intake of study drug in the DB Period.

If the Visit 3 value is not-missing, and not 0, then percentage change will be calculated as: (Change from Baseline / Visit 3 Value) * 100%.

Change from End of Double-Blind Period and Percentage Change from End of Double-Blind Period

For all efficacy and safety endpoints in the Part 1 OL Period, the Change from the End of DB Treatment Period will be calculated as Observed Value in OL Period – End of DB Period Value, where the End of DB Period value will be: 1.) either the last collected value collected in the DB Period up to and including the date of the Visit 4, or 2.) for the Weekly Cataplexy Attacks endpoint, the Weekly Cataplexy Attack Count from the DB Period will be used.

If the end of DB Period value is not-missing, and not 0, then percentage change will be calculated as: (Change from Baseline / End of DB Period Value) * 100%.

Change from the Start of Part 2 Open Label Continuation and Percentage Change from Start of Part 2 Open Label Continuation

For vital sign assessments and physical stature assessments in the open label continuation period in Part 2, the change from the start of the Part 2 OL period will be calculated as Observed Value in OL Continuation Period – Start of OL Continuation Period. For subjects who continued directly from Part 1 to Part 2, the value at Visit 15 will be used as the start of OL Continuation. For subjects who re-enrolled into Part 2, the last non-missing value collected on or prior to Visit 18 will be used as the start of OL Continuation.

If the end of Start of OL Continuation value is not missing, and not 0, then percentage change will be calculated as: (Change from Baseline / Start of OL Continuation Period) * 100%.

Age at First Study Drug Dispensation

Age will be calculated at the date of Study Day 1.

For countries where regulations allow only the year of birth to be entered for birth date, July 1st of that year will be used for the calculation of age. In the event an age calculated using this imputed birth date results in an age of 6 years, then the age will be assigned as 7.

The SAS function YRDIF will be utilized to calculate the age.

AGE = FLOOR(YRDIF(DOB, STRTDT, 'AGE')), where DOB is the date of birth and STRTDT is the date of Study Day 1.

Age at Start of Part 2 OL Continuation Period

For subjects who enter Part 2 and take at least one dose in the OL Continuation Period, the age at first dose in Part 2 will be calculated. The same formula for calculation of age at first study drug dispensation will be used.

Age Group

Age at first study drug dispensation will be categorized into age groups of 7-11 or 12-17. Deviations from protocol Inclusion Criterion #1, requiring subjects to be 7-16 years of

age at Visit 2, are unexpected. If a deviation does occur, then subjects aged less than 7 will be categorized into the 7-11 age group and subjects aged older than 17 at entry will be categorized into the 12-17 age group.

The age at start of OL Continuation (Part 2) will also be categorized as 7-11 and 12-17 years.

Years from Narcolepsy Diagnosis

Years from Narcolepsy diagnosis will be calculated using the screening visit date. For subjects with partial dates for the narcolepsy diagnosis, the years since diagnosis will be calculated by assuming the earliest date implied by the portions of the date available, unless that implied date is prior to the date of birth. If that situation occurs, the date of birth will be used for determining the years since diagnosis.

Years = (ScrDt – DXDT + 1) / 365.25, where ScrDt is the date of the screening visit and DXDT is the diagnosis date or imputed diagnosis date. Values will be rounded to one decimal.

7.3. MISSING DATA

Missing Efficacy Data for the DB Period

Missing efficacy endpoints for the weekly number of cataplexy attacks or weekly school attendance during the whole DB period will be imputed. Methods for derivation for the parameters are described in Section 9. In the event that there are no cataplexy diary entries completed in the DB Period, the value computed for the SD Period will be carried forward as the DB Period value (i.e. baseline value carried forward).

For the ESS (CHAD), SF-10 Physical Summary Score, and SF-10 Psychosocial Summary Score endpoints, a missing value in the DB Period will be imputed using the last available value from the SD Period (i.e. baseline value carried forward).

Adverse Event Data

Adverse event onset date, when a partial date has been provided, will be imputed using the following algorithm, defined to assign AEs to have occurred in a treatment period, if possible, and to assign the onset to the earliest applicable treatment period.

If the year of onset only is provided and the year is the same as the year of first dose, then the date of first dose will be imputed as the onset date. If the year of onset is strictly greater than the year of first dose or strictly less than the year of first dose, then January 1st of the year provided will be imputed.

If the month and year of onset are provided, and the month and year are equal to the month / year of first dose, then the date of first dose will be imputed as the onset date. In all other cases, the 1st day of the provided month/year of onset will be imputed for the onset date.

AEs with missing severity will be summarized separately.

AEs with missing relationship to study treatment will be considered to be related to or suspected to be related to study treatment.

In the situations where a partial onset date is provided, this imputed onset date will be utilized for determination of the period of onset for presentation of the summaries of the AEs. Partial onset dates will be presented as collected in the listings. Similarly, AEs with missing severity or relationship will be presented as missing in the listings.

Concomitant Medications Data

For concomitant medications with incomplete start dates, the start date will be imputed using the earliest possible date implied by the portions of the date provided.

If the year of start only is provided, then January 1st of that year will be imputed for the start date, unless January 1st of that year is prior to the subject's date of birth. In that case, the date of birth will be imputed as the start date.

If the month and year of start are provided, the 1st day of the provided month/year of onset will imputed for the onset date, unless that imputed date is prior to the subject's date of birth. In that case, the date of birth will be imputed as the start date.

Incomplete concomitant medication end dates will be imputed using the latest possible date implied by the portions of the date provided.

If the year of end only is provided, December 31st of that year will be imputed as the end date. If that date is after the subject's termination from the study date, then the study termination date will be imputed for the medication end date.

If the month and year of end are provided, then the last day of that month will be imputed as the end date. If that date is after the subject's termination from the study date, then the study termination date will be imputed for the medication end date.

An individual medication may be classified as having been used in multiple periods.

7.4. VISIT WINDOWS FOR EARLY TERMINATION

Early termination visits that occur in the DT Period will be placed into analysis visits based on the following windows based on calculated study day and protocol defined windows. Windows for the early termination visits in the DT Period are defined as:

Visit	Scheduled Study Day (calculated from Study day 1)	Start of Window	End of Window
Visit 1.2 (Week 1)	7	1	10
Visit 1.3 (Week 2)	14	11	17
Visit 1.4 (Week 3)	21	18	24
Visit 1.5 (Week 4)	28	25	31
Visit 1.6 (Week 6)	42	32	45
Visit 1.7 (Week 8)	56	46	63
Visit 2 (Week 10)	70	64	No upper bound

Early termination visits that occur in the OL Period in Part 1 will be placed into analysis visits based on the following windows based on calculated study day. Windows for the early termination visits in the OL Period are defined as:

Visit	Scheduled Study Day (calculated from Study day 1)	Start of Window	End of Window
Visit 5 (4 Weeks after end of Double-Blind Period) – for Xyrem Naïve subjects	28 days after Visit 4, day 98 at latest	Visit 4 Date + 1	105
Visit 5 (Week 9) for subjects on Xyrem at entry	63	Visit 4 Date +1	70
Visit 6 (Week 16)	112	106 (Xyrem Naïve)/71 (on Xyrem at entry)	119
Visit 7 (Week 18)	126	120	133
Visit 8 (Week 22)	154	134	161
Visit 9 (Week 26)	182	162	189
Visit 10 (Week 30)	210	190	217
Visit 11 (Week 34)	238	218	245
Visit 12 (Week 39)	273	246	280
Visit 13 (Week 43)	301	281	308
Visit 14 (Week 48)	336	309	343

Visit	Scheduled Study Day (calculated from Study day 1)	Start of Window	End of Window
Visit 15 (Week 52)	364	344	No upper bound

Early termination visits that occur in the OL Continuation Period (i.e. Part 2) will be placed into analysis visits based on the following windows based on calculated study day from first dose date in Part 2. Windows for the early termination visits in the OL Continuation Period are based on the every 3 month onsite visits. They are defined as:

Visit	Scheduled Study Day (calculated from Study day 1)	Start of Window	End of Window
Visit 21 (Month 3)	90	1	97
Visit 24 (Month 6)	180	98	187
Visit 27 (Month 9)	270	188	277
Visit 30 (Month 12)	360	278	367
Visit 33 (Month 15)	450	368	457
Visit 36 (Month 18)	540	458	547
Visit 39 (Month 21)	630	548	637
Visit 42 (Month 24)	720	638	no upper limit

7.5. POOLING OF CENTERS

Centers will be pooled into Country Groups (US, and Europe).

Sites will be pooled into Site Groups (Site 112, Site 401, and Other Sites).

7.6. SUBGROUPS

For all efficacy endpoints except school attendance, subgroup analyses in the DB Period will be provided by Age Group, Xyrem Status at Study Entry, Country Group, and Site Group.

For the following safety analyses, subgroup analyses in the DB Period will be provided by Age Group and Xyrem Status at Study Entry:

- TEAEs by SOC/PT
- Labs (eg., hematology, liver function, chemistry, growth hormones)
- Vitals
- Physical stature
- ECG

8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS, AND MEDICATION

8.1. SUBJECT DISPOSITION AND WITHDRAWALS

The number of subjects enrolled into the study and each of the periods along with disposition will be summarized using the subjects in the Safety Population or Randomized Population for each period as appropriate.

For the DB Period, a comparison between treatments of the percentage of subjects who discontinued will be performed using a Pearson's Chi-square test. This test will include only those subjects who were randomized prior to the implementation of Amendment 4.

For the disposition tables for Part 1, the reasons for early termination include: Lack of Efficacy, Protocol Violation, Adverse Event, Death, Withdrawal of Consent/Assent, Cataplexy Instability during Stable-Dose Period, Dose Instability during Stable-Dose Period, Lost to Follow-Up, Treatment Non-Compliance, Diary Non-Compliance, Sponsor Decision, Investigator Decision, and Other. The reasons of Cataplexy Instability during the Stable-Dose Period and Dose Instability during Stable-Dose Period will only be presented for the terminations in the SD Period.

For Part 1, the number of subjects by country, study site/investigator will be summarized for the Safety Population. The summarization will be done by Age Group, Xyrem Status at Study Entry, and Total.

The number of subjects who entered the DB Period will be summarized by the treatment assigned during the period. The summarization will be done by Age Group, Xyrem Status at Study Entry and Total. This summarization will be done using the Safety Population who were dispensed Study Drug during the DB Period.

The number of subjects in each of the study populations will be summarized by Age Group, Xyrem Status at Study Entry and Total.

For subjects who completed Part 1 of the study after Amendment 5 was implemented, the number of subjects who did not enter Part 2 will be presented by Age Group.

For the disposition table for Part 2, the reasons for completion of the study as well as reasons for early termination will be summarized. Reasons for completion of Part 2 include: Subject turns 18 years, US FDA decision on the addition of pediatric data to the Xyrem US PI, and Subject completed additional 2 years. Reasons for early termination in Part 2 include: Lack of Efficacy, Protocol Violation, Adverse Event, Death, Withdrawal of Consent/Assent, Lost to Follow-up, Treatment Non-Compliance, Sponsor Decision, Investigator Decision, and Other.

For Part 2, the number of subjects who entered the Part 2 OL Continuation Period by country, and study site/investigator will be summarized using the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period.

8.2. DEMOGRAPHIC AND OTHER BASELINE DISEASE CHARACTERISTICS

For Part 1, demographic data, including age, sex, race, ethnicity, country, and country group will be summarized for the Safety Population, PK Half-Dose Population, PK Full Dose, PK Completer Population, Safety Population who had Drug Dispensed in the Double-Blind Treatment Period, and Efficacy Population. For categorical variables, missing values will be presented in a row labeled "Missing". Percentages will be calculated using the number of subjects in the population.

For the Safety Population who took Drug in the Part 2 Open Label Continuation Period, the demographic data at initial study entry age at first dose in Part 2, sex, race, ethnicity, country, and country group will be summarized.

For Part 1, baseline disease characteristics, including: Xyrem status at entry (i.e. Xyrem Naive vs. On Xyrem at entry), years from narcolepsy diagnosis to study entry, narcolepsy symptoms experienced prior to any narcolepsy treatment, current narcolepsy symptoms, months of previous Xyrem exposure for subjects on Xyrem at study entry, subjects whose typical nighttime administration of 2 Xyrem doses was unevenly split, Tanner Stage at Screening, CGIs for Historical Narcolepsy Severity Prior to Any Narcolepsy Treatment, CGIs for Historical Cataplexy Severity Prior to Any Narcolepsy Treatment, CGIs for Narcolepsy overall at baseline, CGIs for Cataplexy Severity at baseline, typical bedtime, typical awaking time, usual hours of sleep per night, SF-10 Physical Summary Score, SF-10 Psychosocial Summary Score, and Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD]) score, will be summarized for the same analysis populations noted for the demographic characteristics. The last non-missing assessment prior to or on Study Day 1 will be provided for SF-10 and ESS [CHAD]. The narcolepsy symptoms experienced prior to any narcolepsy treatment and currently summarized include: cataplexy, excessive daytime sleepiness, hypnagogic and/or hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep.

Usual hours of sleep will be determined using the data provided on the Xyrem regimen history eCRF for subjects on Xyrem at entry and the Usual Bed and Awakening Times eCRF for subjects who were Xyrem Naïve at entry. Bedtimes and awakening times are recorded with 24 hour clocks.

The CGIs values are rated by the investigator. The CGIs for Historic Narcolepsy Severity and CGIs for Historic Cataplexy Severity rate the subject's disease prior to any narcolepsy treatment. The CGIs for Cataplexy severity and Narcolepsy severity rate the

subject's condition at the time of the current visit. Responses go from 0 = Normal; no signs of illness, 1 = Borderline ill, 2 = Slightly ill, 3 = Moderately ill, 4 = Markedly ill, 5 = Severely ill, to 6 = Among the most extremely ill.

Details for calculation of the ESS [CHAD] score and SF-10 scores are contained in Sections 9.2.2 and Section 9.2.4, respectively.

Baseline characteristics will be summarized using the Safety Population who had Study Drug Dispensed during the Double-Blind Treatment Period, PK Half-Dose Population, PK Full Dose, PK Completer Population, and Efficacy Population. For the Safety Population who had Study Drug Dispensed during the Double-Blind Treatment Period and Efficacy Population, differences in means between the two randomized treatments for continuous variables will be compared using a one-way ANOVA using treatment group as a factor. The comparison of the two randomized treatments for non-ordinal categorical endpoints will be done using a Pearson's Chi-square test. The comparison of treatments for ordinal categorical variables will be compared using a Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference. Races with small frequencies may be collapsed for the Pearson's Chi-Square test. Inferential comparisons of treatment groups will include only those subjects who were randomized into the DB Period prior to the implementation of Amendment 4.

For the Safety Population who Took Drug in the Part 2 Open-label Continuation Period, the following baseline characteristics will be summarized: Xyrem status at entry, Part 2 subject type, and the duration (days) between the last dose date in Part 1 and the first dose date in Part 2. The Part 2 Subject types include: Subject Continuing directly into Part 2, Re-enrolling and did not require titration, and Re-enrolling and required titration.

8.3. MEDICAL / SURGICAL HISTORY

During Part 1, Medical and surgical history, excluding narcolepsy and cataplexy, are recorded on the Medical/Surgical History eCRF. At the screening visit, the investigator indicates body system, diagnosis or condition or surgical procedure, onset date, end date, and indicates whether the condition is still ongoing. The medical history data are not being coded to any medical dictionary (e.g. Medical Dictionary for Regulatory Activities (MedDRA)).

For Part 1, the Medical / Surgical History body systems will be summarized for the Safety Population and Safety Population who had Study Drug Dispensed in the Double-Blind Treatment Period. Summarization will be done by Age Group, Xyrem Status at Study Entry, and Total. Summarization for the Safety Population who had Study Drug Dispensed during the Double-Blind Treatment Period will be done by Randomized Treatment Group, OL Xyrem, and Total.

The Medical / Surgical History terms will be provided in a listing. For subjects who re-enrolled into the study for Part 2, a column will be added to indicate terms that were entered into the Medical / Surgical History after completion of Part 1 and prior to enrollment in Part 2. Within subject number, the terms will be sorted by the Study Part (Part 1 vs. Part 2), investigator reported Body System, and investigator provided term.

8.4. MEDICATIONS

Medication usage (other than Xyrem) is collected on the Concomitant Medication eCRF. Medications will be coded using the WHO Drug dictionary (Version March 1, 2014). ATC classification of each medication will also be provided. The medication name, start date, start time (if available), stop date, stop time (if available), dosage, route of administration, and indication are collected. Medications will be classified as being used in one/or more study periods according to the rules described in Section 7.1. Time of start of usage/time of end of usage, if provided, will not be utilized in the determination of which period(s) the medication was used.

Prior medications are defined as those medications started prior to Study Day 1, including medications continuing on or after Study Day 1.

Prior medications will be summarized using the ATC Level 4 terms and the preferred names for the Safety Population.

Concomitant medications used during each of the study periods (DT, SD, DB, OL, Period between end of OL and Start of OL Continuation Period, and OL Continuation Period) will be summarized using the ATC Level 4 terms and preferred names.

For all medication tables, ATC Level 4 terms will be sorted alphabetically. Within ATC Level 4 terms, preferred names will be sorted in descending order of overall incidence.

A listing of medications used will be provided, identifying the period(s) of usage.

Stimulant Usage

Usage of stimulants during the SD Period and DB Period will be assessed using the evening cataplexy frequency diaries and the responses to the questions “Did you take a stimulant today?” and “Reason stimulant was not taken”.

A subject will be considered as “supposed to have taken stimulant” during the period if the response to the first stimulant question (i.e. did you take a stimulant today?) was yes, or the response to the reason stimulant was “I was supposed to take stimulant, but I didn’t” on any single day during the period.

The percentage of subjects who took all their stimulants during the period, the percentage of subjects who were supposed to take stimulants and only took stimulants part of the period, and the percentage of subjects who were supposed to take stimulants but didn't take any will be determined.

The summary for the SD Period will be determine using the diaries starting the day after Visit 2 and ending with the diary collected on the date of Visit 3. The summary for the DB period will be determined using the diary started the day after Visit 3 and ending with the diary collected on the date of Visit 4.

Flavorant Usage

Summaries of flavorant usage in Part 1 will be completed using the Safety Population who Took Study Drug. Dispensing of flavorant along with the study medication is reported by Bracket in their dispensing report. The intake of the flavorant is optional. For Part 1 visits during DT, SD, DB, and OL combined, the number of subjects who had flavorant dispensed at < 50% of their dispensing visits vs. ≥ 50% of their dispensing visits will be completed by Age Group, Xyrem status at Entry, and overall. Further, the number of visits where flavorant was dispensed to the subject will be done categorically.

A similar analysis of flavorant usage in Part 2 will be completed using the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period. The summary will be done by Age Group at Entry into the study and overall.

8.5. PROCEDURES

Concomitant procedures are collected on the procedure eCRF. Procedures will be coded using the MedDRA dictionary version 17.0. The procedure name, start date, start time (if available), and indication are collected. Procedures will be classified as being in one of the study periods according to the rules described in Section 7.1. Procedure time, if provided, will not be utilized in the determination of which period the procedure occurred.

A listing of procedures will be provided, identifying the period(s) of occurrence.

No other summarization of concomitant procedures is planned.

9. EFFICACY

Prior to Amendment 4, 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.

The DSMB recommended stopping placebo treatment during Double-Blind Randomized-Withdrawal Period due to the positive primary efficacy results from the pre-specified interim analyses. Since the primary efficacy endpoint was reached and the placebo treatment is discontinued, significance testing will be conducted starting at the Tier 2 endpoint as defined below, using two-sided testing at each Tier.

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 DB Treatment Period.

The primary endpoint demonstrated efficacy at the interim analysis with a significance level <0.005, using methods described in Section 9.1.2.2. A nominal p-value will be provided. Testing will continue with Tier 2.

Tier 2: Key secondary endpoint #2

2. CGIc for cataplexy severity from the end of the SD Period to the end of the DB 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

3. Change in the ESS (CHAD) score from the end of the SD Period to the end of DB 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 SD Period to the end of the DB 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 Physical and Psychosocial Summary Score) from the end of the SD Period to the end of the DB Period

The testing of the SF-10 endpoints will be conducted using the Hochberg procedure (1995), where the 2 p-values from the tests will be ordered from smallest to largest. The p-values (P(1), P(2)) will be compared to the Benjamini-Hochberg critical value. If the highest p-value is < 0.05, then both tests will be considered statistically significant. Otherwise, if the highest p-value ≥ 0.05 and the smallest p-value is < 0.025 then the hypothesis associated with the smallest p-value will be considered statistically significant.

Inferential testing will only be performed for subjects who were randomized to double-blind treatment and included in the efficacy population for the primary and secondary efficacy endpoints. All other efficacy analyses including sensitivity analyses of efficacy endpoints, exploratory efficacy endpoint analyses and subgroup analyses will be tested without multiplicity adjustments and nominal p-values will be provided.

Unless otherwise specified, summaries will be provided as described in Section 7.1 using the populations as described in section 6. Section 7.3 describes imputation for efficacy parameters.

No efficacy data is collected during Part 2. No analyses of efficacy endpoints for Part 2 will be completed.

9.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint, change in the weekly number of cataplexy attacks, will be determined via the evening cataplexy frequency diary. For Xyrem-Naïve subjects, the diary is collected each evening from the start of the DT Period through the end of the OL Period. For subjects on Xyrem at study entry, the diary is collected each evening during the SD Period through the end of the OL Period. The primary efficacy endpoint is the Tier 1 endpoint. This endpoint is applicable only to Part 1 of the study. The cataplexy frequency diary is not collected during Part 2.

9.1.1. Calculation of Weekly Number of Cataplexy Attacks

Any diary day where the response is “No, I did not have cataplexy today” will count as a completed diary day and that day will count as a 0 in the attack frequency total. Diary days where a numeric frequency of cataplexy events is provided will be counted as a completed diary day and the number provided will contribute to the total number of attacks during the periods.

9.1.1.1. Calculation within the DT Period

The DT Period will be separated into 7 day periods starting from the first dispense of study drug in the DT Period (i.e. Day 1-7, Day 8-14, etc.). For each 7 day period, the weekly number of cataplexy attacks will be determined by counting the total number of cataplexy attacks reported during the period and dividing this sum by the number of days during the period where a diary was completed, and then multiplying this ratio by 7 in order to get a weekly number of attacks.

Also, the weekly number of cataplexy attacks will be determined using the last 7 days of the DT period. The diary collected on the date of Visit 2 will be the last day of this period. If the subject does not have a Visit 2, then the last available collected diary during the DT period will be the last day of the period. The first day in this week would be determined by counting back 7 calendar days from the last diary collection during the period. The days utilized in the calculation of the weekly number in the last 7 days will not be mutually exclusive from the weekly frequency mentioned in the first paragraph of this section.

9.1.1.2. Calculation within the SD Period

The primary calculation of weekly number of cataplexy attacks during the SD Period will be determined using the last 14 days during the SD Period.

The weekly number of cataplexy attacks in the period will be calculated by determining the total number of cataplexy attacks reported during the last 14 days of the SD Period, ending with the diary collected on the date of Visit 3 (End of Stable-Dose Period/Start of Double-Blind Treatment Period), dividing by the number of days during the period where a diary was completed. This ratio is then multiplied by 7 to determine the weekly number of attacks.

As a supplemental analysis of the SD Period cataplexy attacks, the period will be separated into 7 day periods starting with the day after Visit 2 and ending with the diary collected on the date of Visit 3. The determination of weekly cataplexy attacks will be done similar to the calculation of attacks in the DT Period. As well, the weekly number of cataplexy attacks will be determined using the last 7 days of the SD Period.

9.1.1.3. Calculation within the DB Period

The primary analysis of weekly number of cataplexy attacks during the DB Period will be calculated using all diaries reported during the period starting from the day after the start of the DB Period through the date of Visit 4 (End of Double-Blind Treatment Period/Beginning of Open-Label Safety Period). The weekly number of cataplexy attacks during the DB Period will be calculated by counting the total number of cataplexy

attacks reported during the period starting from the day after the start of DB Period through the date of Visit 4 (End of Double-Blind Treatment Period/Beginning of Open-Label Safety Period), dividing by the number of days during the period where a diary was completed. This ratio is then multiplied by 7 to determine the weekly number of attacks. The baseline value for the weekly number of cataplexy attacks for the DB Period is the value calculated for the last 14 days of the SD Period. Change from baseline will be calculated as weekly number of cataplexy attacks during the DB Period – weekly number of cataplexy attacks during the SD Period.

As a supplemental analysis of the DB Period cataplexy attacks, the period will be separated into 7 day periods starting with the day after the start of the DB Period and ending with the diary collected on the date of Visit 3 through the date of Visit 4. The determination of weekly cataplexy attacks will be done similar to the calculation of attacks in the DT Period. As well, the weekly number of cataplexy attacks will be determined using the last 7 days of the DB Period. Missing value imputation will not be used for this supplemental analysis.

For the weekly summaries of attacks in the DB Period, the baseline value is the value calculated for the last 14 days of the SD Period. Change from baseline will be calculated as weekly number of cataplexy attacks during the DB Period – weekly number of cataplexy attacks during the SD Period.

9.1.1.4. Calculation within the OL Period

The weekly number of cataplexy attacks during the OL Period will be calculated in a similar method as the DT Period. The OL Period will be separated into 7 day periods, starting from the date after the first dispense of OL treatment.

Similar to the DT Period calculation, a weekly number of cataplexy attacks will also be calculated for the last 7 days in the OL Period. The baseline value for the weekly number of cataplexy attacks for the OL Period is the value calculated for the SD Period. Change from baseline will be calculated as weekly number of cataplexy attacks during the OL Period – weekly number of cataplexy attacks during the SD Period.

9.1.2. Primary Efficacy Endpoint Analyses

9.1.2.1. Analysis of DB Period

The observed weekly number of cataplexy attacks during the DB Period and change from baseline will be analyzed and summarized using the Efficacy Population (including subjects randomized prior to implementation of Amendment 4).

Statistical testing for a difference between Xyrem and Placebo will be completed using a non-parametric analysis of covariance (ANCOVA) with a two-sided test (Conover, Iman 1981). This is completed by ranking both the baseline covariate and the change from baseline value without regard to assigned treatment group. In the event of ties in the baseline or change from baseline, average ranks are used. The ranks are used in the ANCOVA with the rank for the change from baseline as the dependent variable, treatment as a factor, and the rank for the baseline value as the covariate.

Example SAS code for the modeling is shown below.

```
PROC RANK DATA=ANAL OUT=RANKED TIES=MEAN;
  VAR BASE CHG;
  RANKS RBASE RCHG;
RUN;

PROC GLM DATA=RANKED;
  CLASS TRT01PN;
  MODEL RCHG = TRT01PN RBASE / SS3;
RUN;
```

A histogram augmented with a kernel distribution of the change from baseline in weekly number of cataplexy attacks during the DB Period will be presented.

Sensitivity analysis of the primary endpoint will include:

- Including the stratification factor of Age Group to the PROC GLM model noted above.
- Analysis using the per protocol analysis set

Subgroup analyses of the primary endpoint will be completed, including the non-parametric ANCOVA and histograms. Any p-values presented for the subgroup analysis will be considered exploratory.

9.1.2.2. Interim Analysis of the DB Period

The interim analysis was completed after 35 randomized subjects completed or discontinued early from the DB Period.

The interim analysis was performed by an [redacted] biostatistician not directly involved with the design and analysis of the study. The data were reviewed by the DSMB. The possible recommendations that the DSMB considered were whether to

continue the study or to stop it early considering the objectives of the study and subjects' safety. Considerations for stopping the study early included the following:

For stopping the study early because of treatment success, so that fewer subjects will be exposed to placebo: The O'Brien-Fleming approach was used with the primary efficacy endpoint. This endpoint was tested at a two-sided significance level of 0.005 at the interim analysis.

If statistical significance was shown, the DSMB could recommend stopping the study considering the overall study objectives and subject's safety. If the study was not stopped, to maintain an overall alpha of 0.05, the final analysis was to 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 had not been rejected at the 0.005 significance level, then a futility analysis was to be conducted. The conditional power approach was to be used.

Assuming the trend in the data observed up to the interim analysis would 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 was to be calculated. If the conditional power was less than 15%, it was to be concluded that the study was unlikely to demonstrate efficacy and the DSMB may recommend stopping the study considering the overall study objectives and subjects' safety. The study could have been discontinued early due to futility.

Conditional power at the time of the interim analysis was calculated using the B-value method (Lan and Wittes, 1988).

Let *f* be the information fraction (i.e. the proportion of planned subjects at the time of the interim analysis) = n / 70. "n" will be the total number of subjects in the efficacy population among both randomized treatment groups at the time of the interim analysis.

An LS Means statement for the difference between treatment groups from the ANCOVA model on ranks will be used to provide the Z statistic at the time of the interim analysis for the conditional power, Z_n. Let the B value be

$$B(f) = Z_n * \sqrt{f}$$

The conditional power, at the current trend, will be calculated as:

$$1 - \Phi[\frac{\left(Z_{\alpha/2} - (\frac{B(f)}{f})\right)}{\sqrt{1-f}}]$$

where Φ is the cumulative normal distribution, $Z_{\alpha/2}$ is the Z value from a normal distribution for rejection at the final analysis, in this case $Z_{(0.048/2)}$.

9.1.2.3. Additional Analyses of Cataplexy

Summaries of the number of cataplexy attacks will be completed for the DT, SD, and OL Periods. Summaries in the DT and OL periods will be done by 1 week periods and for the last 7 days of the period. Supplemental summaries of the SD and DB periods will be done by 1 week periods and for the last 7 days of the period.

Supplemental summaries of the number of cataplexy attacks will be completed for the SD and DB period using the 7 day period summaries.

A separate summary of the number of cataplexy attacks during the DB period using subjects who received Open-Label Xyrem in the DB Period.

Graphical presentations of weekly cataplexy frequency along with bars representing the median and interquartile range (IQR) will be created over all dosing periods. This presentation will be done using the Safety Population who took Study Drug during the study. For the DB Period, the presentation will be separated for those randomized to Placebo, those randomized to Xyrem and those assigned OL Xyrem in the DB Period. Similar presentations by Age Subgroup and Xyrem Status Subgroup will be presented.

9.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

9.2.1. Clinical Global Impression of Change (CGIc) for Cataplexy Severity

CGIc for cataplexy severity is the Tier 2 endpoint.

The CGIc for cataplexy severity is collected at the end of the DB Period of Part 1. The CGIc for cataplexy severity is not collected during Part 2. The investigator rates their impression of any change in severity of a subject's cataplexy severity using the rating scale (score) of:

- Very Much Improved (3)
- Much Improved (2)
- Minimally Improved (1)
- No Change (0)
- Minimally Worse (-1)

- Much Worse (-2)
- Very Much Worse (-3)

The summarization will include a frequency analysis showing percentage by category within treatment group. Percentages will be based on those subjects with an observed value for the assessment. Subjects with missing values are not included in the inferential testing but will be identified in a row labeled "Missing". Percentages will be calculated using the number of subjects with a value for the CGIc.

A CMH test for Row Mean Scores Difference will be used to test the CGIc endpoint. There will be no stratification factors used in the analysis.

Example SAS code for the modeling is shown below.

```
PROC FREQ DATA=ANAL;
  TABLE TRT03PN * AVAL / CMH2 SCORES=TABLE;
RUN;
```

Descriptive statistics of the ordinal scores (-3 to 3), including mean and standard deviation) will also be provided as an aid for interpretation.

The number and percent of subjects of CGI-C responders defined as "much improved" or "very much improved" will be summarized. A chi-square test will be performed. The p-value will be considered exploratory.

9.2.2. Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD])

The ESS [CHAD] is the Tier 3 endpoint.

The ESS [CHAD] 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. The responses to each of the 8 questions have the following possibilities: Would never fall asleep, slight chance of falling asleep, moderate chance of falling asleep, and high chance of falling asleep. These responses are scored as 0, 1, 2, and 3 respectively. The ESS [CHAD] score is calculated as the sum of the response scores for the 8 questions resulting in a total score from 0 to 24 (Johns, 1991). If a subject does not complete all 8 questions during an assessment, the ESS [CHAD] score at the assessment will be set to missing.

ESS [CHAD] scores will be categorized as follows:

- 0-10 = Normal
- 11-12 = Mildly Increased
- 13-15 = Moderately increased
- ≥ 16 Greatly Increased

Summarizations of ESS [CHAD] will be completed for the DB and OL Periods of Part 1. The ESS [CHAD] is not collected during Part 2.

For the DB Period, the non-parametric ANCOVA model, used for the primary endpoint, will be used. The p-value from the ANCOVA will be used as the Tier 3 endpoint testing.

A sensitivity analysis will be used adjusting for use of stimulants in the SD period. This will be included as a Yes/No variable based on whether the subject was supposed to take stimulants during the last 14 days of the SD period according to the dosing diary.

9.2.3. Clinical Global Impression of Change (CGIc) for Narcolepsy Overall

CGIc for narcolepsy overall is the Tier 4 endpoint.

The CGIc for narcolepsy overall is collected at the end of the DB Period of Part 1. The CGIc for narcolepsy overall is not collected during Part 2. The investigator rates their impression of any change in severity of a subject's overall condition of narcolepsy using the CGIc rating scale (score) of:

- Very Much Improved (3)
- Much Improved (2)
- Minimally improved (1)
- No Change (0)
- Minimally Worse (-1)
- Much Worse (-2)
- Very Much Worse (-3)

The analyses described for the CGIc for Cataplexy Severity will be used for this CGIc endpoint.

9.2.4. Quality of Life (QoL) (SF-10)

The SF-10 Physical Summary Score (PHS-10) and Psychosocial Summary Score (PSS-10) final are the Tier 5 endpoints.

The SF-10™ Health Survey for Children 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 (QualityMetric, 2007).

For subjects on Xyrem at entry, the SF-10 is collected at Visits 2, 3, 4, 5, 7, 9, 12, 15, or Early Termination (if applicable) of Part 1. For Xyrem Naïve subjects at entry, the SF-10 is collected at Visits 1.1, 3, 4, 5, 7, 9, 12, 15 or ET of Part 1. The SF-10 is not collected during Part 2.

9.2.4.1. Scoring the SF-10

Each of the 10 questions responses is scored with a point value from 1 to 6, so that 1 is the worst possible condition and 6 is the best possible condition. Mapping of the question responses to point values is as follows:

Question 1: In general, would you say your child's health is:		
Response Choices	**Code**	**Point Value**
Excellent	1	6
Very Good	2	4.75
Good	3	3.5
Fair	4	2.25
Poor	5	1

Question 2a: During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems? **a. Doing things that take some energy such as riding a bike or skating?**		
Response Choices	**Code**	**Point Value**
Yes, limited a lot	1	1
Yes, limited some	2	2.67
Yes, limited a little	3	4.33

Statistical Analysis Plan

Question 2a: During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems? **a. Doing things that take some energy such as riding a bike or skating?**		
Response Choices	**Code**	**Point Value**
No, not limited	4	6

Question 2b: During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems? **b. Bending, lifting, or stooping?**		
Response Choices	**Code**	**Point Value**
Yes, limited a lot	1	1
Yes, limited some	2	2.67
Yes, limited a little	3	4.33
No, not limited	4	6

Question 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?		
Response Choices	**Code**	**Point Value**
Yes, limited a lot	1	1
Yes, limited some	2	2.67
Yes, limited a little	3	4.33
No, not limited	4	6

Question 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?		
Response Choices	**Code**	**Point Value**
Yes, limited a lot	1	1
Yes, limited some	2	2.67
Yes, limited a little	3	4.33
No, not limited	4	6

Question 5: During the past 4 weeks, how much bodily pain or discomfort has your child had?		
Response Choices	**Code**	**Point Value**
None	1	6
Very mild	2	5
Mild	3	4
Moderate	4	3
Severe	5	2
Very severe	6	1

Question 6: During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?		
Response Choices	**Code**	**Point Value**
Very satisfied	1	6

Question 6: During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?		
Response Choices	**Code**	**Point Value**
Somewhat satisfied	2	4.75
Neither satisfied nor dissatisfied	3	3.5
Somewhat dissatisfied	4	2.25
Very dissatisfied	5	1

Question 7: During the past 4 weeks, how satisfied do you think your child has felt about his/her life overall?		
Response Choices	**Code**	**Point Value**
Very satisfied	1	6
Somewhat satisfied	2	4.75
Neither satisfied nor dissatisfied	3	3.5
Somewhat dissatisfied	4	2.25
Very dissatisfied	5	1

Question 8: During the past 4 weeks, how much of the time do you think your child acted bothered or upset?		
Response Choices	**Code**	**Point Value**
All of the time	1	1
Most of the time	2	2.25

Question 8: During the past 4 weeks, how much of the time do you think your child acted bothered or upset?		
Response Choices	**Code**	**Point Value**
Some of the time	3	3.5
A little of the time	4	4.75
None of the time	5	6

Question 9: Compared to other children your child's age, in general would you say his/her behavior is:		
Response Choices	**Code**	**Point Value**
Excellent	1	6
Very Good	2	4.75
Good	3	3.5
Fair	4	2.25
Poor	5	1

The questions and associated point values are separated into the PHS-10 domain (5 questions; questions 1, 2a, 2b, 3, and 5) and PSS-10 domain (5 questions; questions 4, 6, 7, 8, 9). The sum of the scores in the domain (PHS-10 agg and PSS-10 agg) will be standardized using the mean and standard deviation from a normal population (2006 sample).

PHS-10 standard = (PHS-10 agg – 27.3525139) / 3.6706635.

PSS-10 standard = (PSS-10 agg - 24.2583251) / 4 .6749490.

The final scores will be calculated by transforming the standardized scores to the norm-based scoring (NBS) metric.

PHS-10 final = (PHS-10 standard x 10) + 50

PSS-10 final = (PSS-10 standard x 10) + 50

For the statistical analysis, the final scores will be rounded to one decimal of accuracy.

Summary aggregate scores, standard scores, and final scores at an assessment will be calculated only if all questions within the domain are answered.

The summary of results in the DB Period will be conducted using the same methodology as used for the primary endpoint. A summary of the OL Period results will also be completed.

Descriptive, frequency summaries of the 10 individual questions will be performed.

The inferential analysis will be performed using the Efficacy population for the summary aggregate scores.

9.3. EXPLORATORY EFFICACY ENDPOINT(S) AND ANALYSES

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

9.3.1. Weekly School Attendance

9.3.1.1. Calculation of Endpoint

In Part 1, the school attendance diary is collected from subjects who attend school during the last two weeks of the SD Period and during the DB Period. The school attendance diary is not collected during Part 2. The diary collects whether the child was scheduled to attend school on the day and whether the child missed school that day due to narcolepsy.

For the SD Period and DB Period of Part 1, the percentage of school days missed due to narcolepsy will be calculated as: (the count of days missed / the count of days where the child was scheduled to attend) x 100%. This value will be calculated only if a subject has submitted a diary indicating that they were scheduled to attend school on at least one day during the period.

The % of days missed will be calculated only if the total number of days the subject was scheduled to attend during the period (using available, collected diary days) is at least 7. The change in percentage missed will be calculated as the percentage of days missed in the DB Period minus the percentage of days missed in the SD Period.

The analysis of school attendance will be presented only for subjects in the Efficacy Population who have school diaries in both the SD Period and DB Period. A separate, descriptive summarization will be performed using those subjects who received Open-Label Xyrem during the DB Period, and have school diaries in the SD Period and DB Period.

Observed values and change from baseline in the percentage of days missed will be summarized using the same methodology as the primary endpoint.

9.3.2. PGIc for Narcolepsy Overall

During Part 1, the PGIc for narcolepsy overall is collected at the end of the DB Period or ET visit, if the subject discontinues in the DB Period. The PGIc for narcolepsy overall is not collected during Part 2.

The subject is asked to respond to the question "How would you rate your narcolepsy since Visit 3 (the end of the Stable-Dose Period)?" Responses are from a 7 point scale (score) of:

- Very much better (3)
- Much better (2)
- A little better (1)
- No change (0)
- A little worse (-1)
- Much Worse (-2)
- Very Much Worse (-3)

Summarization of the DB Period will be done using the same method as used for CGIc for Cataplexy Severity.

This analysis will be performed using the Efficacy population. A separate, descriptive summarization will be performed using those subjects who received Open-Label Xyrem during the DB Period.

10. ANALYSIS OF PHARMACOKINETICS

The analysis of PK data will address the Secondary Objective #2.

The collection of PK data is only done during Part 1 of the study.

Summaries by Xyrem dosage will include: by-subject plots of sodium oxybate concentrations and log transformed sodium oxybate concentrations, summaries of sodium oxybate concentrations by collection time, summaries of calculated PK parameters, and analyses of dose proportionality using the Area under the Plasma Time Concentration Curve through 4 hours (AUC_{0-4}), $AUC_{0-infinity}$ and Maximum Plasma Drug Concentration (C_{max}).

10.1. SODIUM OXYBATE CONCENTRATION DATA

Plasma samples for the characterization of sodium oxybate pharmacokinetic profiles are collected during the SD Period or during the OL Period. Samples for the collection of sodium oxybate concentrations are collected on two separate PK nights.

For subjects on Xyrem at study entry participating in the PK assessments in the SD Period, PK Night 1 will occur on the first night of the SD Period and PK Night 2 will occur the next night or within 15 days of PK Night 1.

Prior to Amendment 4, subjects on Xyrem at study entry or Xyrem Naïve subjects at study entry participating in the PK assessments in the OL Period, the PK Night 1 occurred after retitration to a stable dose and there is no restriction on timing of PK Night 2.

After Amendment 4, subject PK assessments could occur at any point in time where the subject was on a stable does of Xyrem.

On the PK night 1, the subject will receive ½ of their usual and current nighttime Xyrem dosage (separated into two equally divided dosages delivered at bedtime and 4 hours later). On the PK Night 2, the subject will receive their usual current nighttime Xyrem dosage (separated into two **equally divided** dosages delivered at bedtime and 4 hours later).

On both nights, samples will be collected pre-dose, 0.75, 1.5, 2.5 and 4 (pre-2nd dose), 4.75, and 8 hours post first Xyrem dose on the PK night. The allowable windows for the sample collections are +/- 5 minutes. Concentration data from first dose on each PK night will be used to calculate sodium oxybate PK parameters (see SAP sections 10.2-10.6). 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 presented as peak and residual exposure associated with the second nighttime dose.

Samples will be summarized by scheduled time point. Elapsed time from dose will be used for the calculation of PK parameters.

All sodium oxybate concentrations recorded below limit of quantification (BLQ) will be imputed with a concentration of 0.

Using the PK Half-Dose Population, concentration data will be presented in listings. Xyrem dosage in (g/night), subject's weight (kg) and BMI (kg/m^2) collected closest to the PK night, actual date/ time of dosing, scheduled collection time, actual date/time of sample collection, elapsed time from first dosing on that PK night, and concentration will be provided. The concentration data and log transformed concentration data will also be presented in by-subject plots with the results of PK night 1 and PK night 2 shown on the same page. A natural logarithmic transformation will be used (i.e. $\log_e$).

Summaries of the concentrations on PK Night 1 will be presented using the PK Half-Dose Population as well as for the PK Full-Dose Population and PK Completer Population. A summary of concentrations by time point on PK Night 1 and PK Night 2 will be presented for the PK Full-Dose Population and PK Completer Population.

By time point summaries will be provided by Age Group, available Xyrem dosage levels (g/night), and overall using scheduled time point. Summary statistics for number of observations, mean, standard deviation, coefficient of variation (CV(%)), median, Q1, Q3, minimum, and maximum values will be presented.

10.2. AREA UNDER THE PLASMA TIME CONCENTRATION CURVE 0-4 HOURS (AUC_{0-4})

The AUC_{0-4} on PK Night 1 and PK Night 2 will be calculated using the samples collected up to and including the scheduled 4 hour (pre-2nd dose) sample, as long as these samples were collected prior to the 2nd nightly dose. The linear trapezoidal rule will be used for the calculation.

$AUC = \sum_1^{k-1}\left(\frac{1}{2}\right) * (C_k + C_{k+1}) * (t_{k+1} - t_k)$, where k=1, 2, .., n are the collection numbers, C_k are the concentration values and t_k are the elapsed time in hours from the first dose of Xyrem on the PK night. Scheduled pre-dose samples will have 0 used for the elapsed time from dosing for calculation of AUC values.

If the subject does not have a sample collected at the 4 hour time point, the AUC_{0-4} will not be calculated.

AUC_{0-4} Summaries

Summaries of the AUC_{0-4} on PK Night 1 will be completed, using the PK Half-Dose Population, PK Full-Dose Population and PK Completers Population, by Age Group, available Xyrem dosage levels (g/night), and overall. A summary of AUC_{0-4} on PK Night 1 and PK Night 2 will be completed using the PK Full-Dose Population and PK Completer Population. Summary statistics presented will include the number of observations (n; number of AUC_{0-4} values), Mean, Standard Deviation, CV (%), Geometric Mean, Geometric Standard Deviation, Median, Minimum and Maximum.

Dose Proportionality

For subjects in the PK Completer population, analyses for dose proportionality will be performed for $AUC_{0-4.}$ The analyses will be done utilizing those subjects with AUC_{0-4} parameters available on both PK night 1 and 2.

For each parameter, the log transformed value on PK night 2 minus the log transformed value on PK night 1 will be the response variable. The natural log function will be used. The estimated mean difference and 90% confidence interval will be back-transformed to ratio scale by exponentiation in order to interpret the results in ratio scale. If the value 2 is contained within the 90% confidence interval, it will indicate proportionality. For the PK Completer population, the subject's AUC_{0-4} on PK night 2 will be plotted against the AUC_{0-4} on PK night 1 as a visual aid for dose proportionality.

Regression Modeling

Regression models will explore the relationship between AUC_{0-4} vs. Xyrem dosage. A repeated measures model will be fit using the AUC_{0-4} parameter as the dependent variable with the first nightly Xyrem dosage in mg/kg, Age Group, and PK night as the fixed effects. A log transformation may be used for the dependent variable. Visit will be considered a repeated effect and compound symmetry specified as the covariance structure. If compound symmetry fails to converge, autoregressive (1) will be used. Regression coefficients will be provided.

AUC_{0-4} values will also be presented with a scatterplot plotting the AUC vs. the first nightly Xyrem dosage in mg/kg. The regression model and scatterplot will be done for the PK Half-Dose Population.

10.3. MAXIMUM PLASMA DRUG CONCENTRATION (C_{MAX})

On each PK night, C_{max} will be determined from post dosing concentrations up to and including the 4 hour post dose, as long as the 4 hour sample was collected prior to or at the same time as the 2nd evening dosing. C_{max} is the defined as the highest concentration

through 4 hours post dose for the subject on the night. The summarization will utilize the same populations and methodology used for the AUC including analyses for dose proportionality and multivariate regression modeling as appropriate.

10.4. PLASMA DRUG CONCENTRATION AT 8 HOURS (C_{8HOURS})

On each PK night, C_{8Hours} will be determined from the post dosing concentration at 8 hours post first dose. The summarization will utilize the same populations and methodology used for the AUC including analyses for multivariate regression modeling as appropriate; however, total nightly dose will be used for analysis purposes.

10.5. TIME TO MAXIMUM PLASMA CONCENTRATION (TMAX)

On each PK night, T_{max} will be determined from post dosing concentrations up to and including the 4 hour post dose. It is defined as the elapsed time from the first dose on the PK night associated with the highest sodium oxybate concentration, measured in hours. Values will be summarized descriptively.

10.6. AREA UNDER THE PLASMA TIME CONCENTRATION CURVE (0-INFINITY) AND HALF LIFE ($T_{1/2}$)

The $AUC_{0\text{-infinity}}$ on PK Night 1 and PK Night 2 will be calculated using the samples collected up to and including the scheduled 4 hour (pre-2nd dose) sample, as long as the samples are prior to the 2nd nightly dose. The linear trapezoidal rule will be used for the calculation of AUC through the last measurable concentration above limit of quantification. Samples after the Cmax time point through the 4 hour sample, which are above limit of quantification, will be used for the terminal phase. If there are at least 3 samples in the terminal phase, a linear regression of log transformed concentration vs. time will be completed. $AUC_{0\text{-infinity}}$ will be calculated as $AUC_{0\text{-Last}}$ + Last Concentration / (-1* slope of the regression line).

The summarization will utilize the same populations and methodology used for the $AUC_{0\text{-}4}$ including analyses for dose proportionality, if appropriate.

The half-life on PK Night 1 and PK Night 2 will be calculated using the slope from the log transformed concentrations vs. time used to determine the $AUC_{0\text{-infinity}}$. $T_{1/2\ will}$ be calculated as log 2 / slope. The natural logarithmic function will be used.

11. SAFETY

Subject safety will be assessed via incidence of AEs, vital signs, physical examinations (including weight and height), 12-lead ECG, PSG parameters, clinical laboratory results, assessments of growth and precocious puberty, C-SSRS, CDI 2: SR[S], and MASC-10 assessments.

Unless otherwise specified, summaries will be provided as described in Section 7.1 using the populations as described in Section 6.

Subgroup analyses for key safety endpoints are provided in Section 7.6.

Analyses of extent of exposure, adverse events, vital signs, physical examinations (including height and weight) will be collected during Part 2. They will be summarized for Part 2 using the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period.

11.1. EXTENT OF EXPOSURE

Exposure to study drug will be summarized separately for the DT Period, SD Period, DB Period, and OL Period.

For the DT Period, the following variables will be summarized:

- starting Xyrem dosage (in g/night and mg/kg/night),
- number of adjustments (upward titrations and reductions),
- cumulative Xyrem dosage (in grams),
- total duration of exposure (in days)

The summarization will be done by Age Group, subject weight at the start of titration (categorized as < 30 kg, ≥ 30 kg - < 45 kg, and ≥ 45 kg) and overall.

For the SD Period, the following variables will be summarized:

- Xyrem dosage level (in g/night and mg/kg/night),
- cumulative dosage received (in grams),
- total duration of treatment in days

For the DB Period, the following variables will be summarized using the actual treatment received:

- starting dosage level dispensed (in g/night and mg/kg/night), noting that the subjects randomized to receive placebo will be receiving a matching placebo,
- cumulative dosage received (in grams),
- total duration of treatment in days

For the OL Period the following variables will be summarized:

- final dosage level used in the period (in g/night and mg/kg/night),
- cumulative dosage received (in grams),
- average nightly dosage during the OL Period (calculated as cumulative dosage and dividing by the duration of treatment),
- total duration of treatment in days

Calculation of dosage in mg/kg/night for DT, SD, and DB period will be completed using the latest weight collected prior to or on the start of each Period. For the OL period, the latest weight collected prior to or on the last dose will be used.

For Part 2, an overall summarization of Xyrem exposure will be completed. The total days of exposure to Xyrem and cumulative total Xyrem exposure (in g) will be summarized using the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period. The duration is defined as last dose date in Part 2 – first dose date in Part 2 + 1 day.

A cumulative exposure summary to Xyrem over Part 1 and Part 2 periods will be completed using the Safety Population who Took Study Drug. The total days of exposure to Xyrem, cumulative Xyrem exposure (in g) will be summarized. A categorical summarization of exposure to Xyrem will be completed, categorizing exposure at the cut points: at least 6 months, at least 1 year, at least 18 months, at least 2 years, and at least 3 years will be provided.

For the total exposure period across Part 1 and the entire study (Part 1 and Part 2), the number of subjects who were treated at the maximum proposed dosage for use in the study will be summarized by age group. The maximum dosage allowable per protocol is shown in Table 1 of the protocol document (in Section 3.1.2) and is determined based on the subject's baseline weight in Part 1. Subjects entering on Xyrem will be assessed

using the same dosing table. The duration in days treated at this maximum dosage will be calculated and summarized. For subjects treated with Placebo during the DB period, the number of days treated in the DB period will not be included in the total exposure days at the maximum assigned nightly dose.

11.2. TREATMENT COMPLIANCE

For Part 1, compliance will be assessed using the parent/subject completed morning dosing diary entries. Percentage compliance will be computed separately for each subject in each period. In Part 2, morning dosing diaries are not collected. Compliances based on dosing diaries will not be calculated for Part 2.

Percent compliance will be calculated as the percentage of doses taken out of the expected number of doses. The number of doses taken will be determined using the morning diary entries completed during the period. It will be assumed that any morning where a dosing diary was not submitted indicates that the doses on that night were not taken. The number of doses expected to have been taken will be calculated as 2 times the number of days in the dosing period.

A second compliance calculation will be completed based on the duration of treatment in the each period, the dosage in g/night that the subject was expected to take based on the exposure log records, and the quantity of study drug (measured in mL) returned at each visit. This will be referred to as Bottle Weight Compliance on the tables and listings. The Bottle Weight Compliance will be determined for each period of Part 1. The Bottle Weight Compliance will be determined in Part 2 for the Subjects in Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period.

Details of calculation of Bottle Weight Compliance are as follows.

The initial quantity of drug in a dispensed bottle is 180 mL. The concentration of Xyrem in a bottle is 500 mg/mL. The returned quantity (in mL) is recorded on the CRF. The difference is the actual quantity of drug taken, in mL.

For both Part 1 and Part 2, each night's expected quantity of drug to be taken, based on the assigned dosage level calculated as D * 1000 / 500, where D is the dosage level in g per administration, 1000 is the number of mg per g, and 500 is the concentration of Xyrem in the solution (in mg/mL).

As an example, if a subject was on a dose of 5 g/night, evenly split into 2.5 g per each nightly administration, the quantity of drug in mL expected to be given at that administration is:

(2.5 g x 1000 mg/g) / (500 mg/mL) = 5 mL.

100 times the ratio of [the quantity taken determined by bottle divided by the calculated amount to be taken based on dosing log] will be the Bottle Weight Compliance.

Compliance and Bottle Weight Compliance will be categorized as < 75%, 75-90%, or > 90%.

For each study period in Part 1, the percent compliance, percent bottle weight compliance, categorized compliance, and categorized bottle weight compliance will be summarized.

For Part 2, the percent bottle weight compliance and categorized bottle weight compliance will be summarized for the following periods:

- Part 2 Day 1 – Visit 21 Month 3
- Visit 21 Month 3 – Visit 24 Month 6
- Visit 24 Month 6 – Visit 27 Month 9
- Visit 27 Month 9 – Visit 30 Month 12
- Visit 30 Month 12 – Visit 33 Month 15
- Visit 33 Month 15 – Visit 36 Month 18
- Visit 36 Month 18 – Visit 39 Month 21
- Visit 39 Month 21 – Visit 42 Month 24
- Overall Part 2 Compliance

Early termination visits in Part 2 will be mapped according to the rules in Section 7.4 and summarized accordingly. For each of these periods, the expected weight to be taken will be determined starting one day after the bottle dispense at the start of the period and ending at the day of the bottle return.

11.3. ADVERSE EVENTS

For Part 1, AEs occurring after patient assent or informed consent and until the last study visit (through the Study Follow-up Visit or early termination) will be recorded on the eCRF. For Part 2, AEs occurring after reconsent or assent for Amendment 5 through completion of the Part 2 visit will be recorded on the eCRF. Terms will be coded to the

MedDRA dictionary version 17.0. Events will be assessed as occurring in treatment periods based on the onset date and the date of first dosing in each of the treatment periods. Treatment emergent AE (TEAE) will be defined for a period. As times of dosing are not reported at the start of each of the treatment periods, onset times will not be considered for determination of the period in which the event occurred. In instances where the subject has reported multiple events with the same preferred term (PT) and the onset date indicates that the events had onsets in different dosing periods, the event will be counted as occurring in each of the periods. Terms will be summarized using the system organ class (SOC) and preferred term (PT).

Events that occurred after consent or assent that have onset dates prior to the first dose in the DT Period (for Xyrem Naïve subjects) or SD Period (for subjects on Xyrem at entry) will be shown in listings but will not be included in any AE summary.

For Part 1, AEs with onset date that are on or after the last dose date and up to and including 30 days after the last dose date will be included in the AE summaries. These events will be allocated to the last treatment period in which the subject took study medication. AEs with onset date more than 30 days after the last dose date in Part 1, but not after the date of first dosing in Part 2, will not be included in the AE summaries but will be displayed in listings. AEs with onset date more than 30 days after the last dose date in Part 2 will not be included in the AE summaries for Part 2 but will be displayed in listings.

Events with completely missing onset dates are unexpected. However, if they occur, they will be classified as having onset in the earliest dosing period implied by the portion of the onset date provided (see SAP Section 7.3).

Drug-related or procedure-related adverse events will be defined based on the investigator's assessment. Events with missing values for relationship to study drug or procedure will be classified as being related to study drug or procedure, respectively.

AEs of special interest will be defined with agreement from the Jazz clinical team and DSMB. The PTs included in this list will be kept in a separate document from this SAP and may be amended by the DSMB or the Jazz clinical team. The list of terms will be finalized prior to the data base snapshot or data base lock for the final analysis, and will include, at least the PTs related to the terms noted in Section 9.9 of the protocol.

- 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

Results across the study are presented by Age Group and Xyrem status at initial study entry for the Safety Population who took study drug. All summarizations of AEs will provide the number and percentage (i.e., subject incidence) of subjects who experienced the event. Subjects who experienced multiple events within the same SOC during a period will be counted once in the SOC summary. Subjects who experienced multiple occurrences of events with the same PT during a period will be counted once in the PT summary. Percentages will be calculated using the total number of subjects in the population.

Separate summaries by the Safety Population who took study drug in the period will be provided for:

- Overall summary of TEAE incidence
- TEAEs with onset in each period by SOC and PT (sorted in descending order of subject incidence)
- TEAEs with onset in each period by PT (sorted in descending order of incidence)
- TEAEs with onset in each period by Maximum Severity (sorted in descending order of incidence)
- Treatment-Related TEAEs with onset in each period (sorted in descending order of incidence)
- TEAEs of Special Interest with onset in each period (sorted in descending order of incidence)Serious TEAEs (sorted in descending order of incidence)
- TEAEs leading to Permanent Withdrawal of Study Drug (sorted in descending order of incidence)

Due to the small number of Serious TEAEs and TEAEs leading to Permanent Withdrawal of Study, these summaries may be presented only in listings.

TEAE summaries across Part 1 will include the following:

- Overall summary of TEAE incidence
- TEAEs by PT while receiving Xyrem (excluding DB Period events for those treated with Placebo during the DB Period)

Combined adverse event summaries across the study (Part 1 and Part 2) will be provided for:

- Overall summary of TEAE incidence
- TEAE by PT, regardless of treatment during the DB period
- TEAE by PT while receiving Xyrem

- TEAEs of Special Interest while receiving Xyrem

11.3.1. Additional AE Analyses

For each period and across the study, the subject incidence of TEAEs will be summarized for each nightly dose level by SOC and PT. The nightly dose will be based on the dose taken the night prior to the start date of the adverse event. For adverse events occurring on Study Day 1, the dose taken the night of the AE will be used.

Additionally, the incidence of TEAEs by SOC, PT, and most recently assigned dosage of Xyrem in mg/kg/night will be provided for the DT period and combining all periods from the SD period onwards. The most recently assigned dosage of Xyrem in mg/kg will be categorized based on the tertiles of Xyrem mg/kg dosage in the SD period for subjects treated in the SD period. The subject incidence and exposure adjusted event rate of TEAEs using SOC/PT (as well as the subset of TEAEs of Special Interest) while on Xyrem will be summarized across the study. The exposure adjusted event rate will be defined as the number of events experienced divided by the number of days of Xyrem exposure. Recurrent AEs are included in the event rates. Results are provided per 100 days of exposure, as it is expected to be easier to interpret given the low rates with patient-days of exposure alone. Therefore, event rates are multiplied by a factor of 100. Events recorded during the DB Period for subjects who received Placebo will not be included. Similarly, the days of exposure during the DB period will not be included in the duration of Xyrem exposure during the DB period for subjects who received Placebo during the period.

11.4. LABORATORY EVALUATIONS

For Part 1, routine blood and urine samples for the assessment of hematology, chemistry and urinalysis parameters are collected at the screening visit, at the end of the DB Period (or early termination), and at the end of the OL Period (or early termination). Abnormal laboratory parameters deemed clinically significant (by the investigator) must be re-evaluated. For Part 2, blood and urine samples for the assessment of hematology, chemistry and urinalysis are only scheduled to be collected at Screening Visit 17 for subjects who re-enrolled in Part 2 after completion of Part 1. Otherwise for Part 2, only available local laboratories results (urine pregnancy test, urine drug screen, and alcohol test) will be provide. These will not be included in any analyses, but will be shown in listings.

For Part 1, assessments of growth and precocious puberty are collected at the Screening visit, End of Stable Dose PSG for Xyrem Naive subjects, Visit 4, and at the end of the OL Period (or early termination). These assessments include: growth hormone, insulin-like growth factor, and prolactin. Sex hormones are collected only for females under 8 years

and for males under 9 years at screening and at the end of the study conduct. Tests for growth and precocious puberty are not scheduled for collection in Part 2.

Samples for coagulation will be collected within 30 days prior to PK Night 1 for those subjects participating in the PK evaluations. Coagulation test samples are not collected in Part 2.

During Part 1, thyroid stimulating hormone (TSH) will be collected at screening for all subjects. TSH is not scheduled for collection in Part 2.

Pregnancy tests will be done for female subjects who reached menarche. During Part 1, these are done at screening, at the start of the DT Period, at the start of the SD Period (for Xyrem experienced subjects), at the end of the DB Period, and at the end of the OL Period. During Part 2, for subjects who re-enrolled in Part 2 after completion of Part 1, pregnancy tests are collected at Visit 17 and Visit 18. For all female subjects in Part 2 who have reached menarche, pregnancy tests are collected every six months and at study completion or early termination. Pregnancy test results will be listed only.

During Part 1, drug and alcohol screening assessments will be collected at screening, at the beginning of the DT Period (for Xyrem Naïve subjects), at the start of the SD Period (for subjects previously on Xyrem), at the end of the DB Period, and during the OL Period. During Part 2, drug and alcohol screenings are collected at Visit 17 and Visit 18, for subjects who re-enrolled in Part 2 after completion of Part 1. For all subjects in Part 2, drug and alcohol screening will be collected every six months. Drug and alcohol screening will be listed only.

Scheduled collections will be assessed by a central laboratory. Follow-up of clinically significant abnormal values may be done by a local laboratory or the central laboratory. For by-visit summaries, only the central laboratory results will be included.

Summarizations for hematology, chemistry, and assessments of growth and precocious puberty, will be done using the results reported in standardized international (S.I.) units.

For Part 1, by visit summarizations of hematology, chemistry, urine pH, and growth hormones will be done using descriptive statistics. Observed values and changes from baseline will be summarized.

For Part 1, summarizations of baseline values will be done using the Safety Population. Additional summaries will be completed for the DB and OL Periods.

For Part 1, summarizations of maximum ratio to upper limit of normal for AST (Aspartate aminotransferase (SGOT)), ALT (Alanine aminotransferase (SGPT)), and Total Bilirubin within the DB Period and OL Period will be conducted.

AST and ALT values will be categorized as:

- ≤ 1 x ULN,
- > 1 - < 3 x ULN,
- ≥ 3 - < 5 x ULN,
- ≥ 5 x ULN

Total Bilirubin values will be categorized as:

- ≤ 1 x ULN,
- > 1 - ≤ 1.5 x ULN,
- > 1.5 - < 2 x ULN,
- ≥ 2 x ULN

For Part 1, occurrences of ≥ 3 x ULN elevations in either AST or ALT accompanied by a ≥ 2 x ULN elevation in total bilirubin (i.e. on the same collection date) will also be summarized.

All laboratory data will be provided in listings. Separate listings will be produced for subjects with at least one abnormal laboratory recording that the investigator has deemed clinically relevant. On these listings, all records that the subject has for the particular test with one (or more) clinically relevant value will be shown and will identify the date/time of collection, visit, period of collection and the indication of clinical relevance. Liver function tests for subjects with at least one of: AST > 3 x ULN, ALT > 3 x ULN, or Bilirubin ≥ 2 x ULN will be displayed on the clinically relevant laboratory result listing. Indications for abnormality and the noted elevations will be made.

11.5. VITAL SIGNS / OXYGEN SATURATION, END TIDAL CO_2 / TRANSCUTANEOUS CO_2

For Part 1, vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (in beats per minute), respiratory rate (breaths per minute), and body temperature, measured in degrees Celsius, are collected at each clinic visit. During Part 2, the SBP, DPB, pulse rate, respiratory rate, and body temperature are collected at Visit 17 and Visit 18 (for subjects who re-enrolled after completion of Part 1), and at the quarterly onsite clinic visits Visit 21 Month 3, Visit 24 Month 6, Visit 27 Month 9,

Visit 30 Month 12, Visit 33 Month 15, Visit 36 Month 18, Visit 39 Month 21, and Visit 42 Month 24 or Early Termination.

For Part 1 and Part 2, summaries of observed values, changes from Part 1 Day 1 baseline, and change from Part 2 Day 1 baseline will be provided for all treatment periods as applicable.

During PSG nights in Part 1, SBP, DBP, pulse rate, respiratory rate, oxygen saturation (SpO_2), End Tidal CO_2 ($EtCO_2$), and Transcutaneous CO_2 are collected prior to the first Xyrem dosage, 1 hour post dose, 4 hours post dose (prior to second Xyrem dosage for the night), 5 hours post first dose, 8 hours post first dose and prior to release from the study center. End tidal CO_2 ($EtCO_2$) or transcutaneous CO_2 ($TcCO_2$) will be monitored and recorded at sites where monitoring is routinely performed and performance will not negatively impact study conduct. PSG sessions are not scheduled for collection in Part 2.

On each PSG night, changes will be calculated from the pre-dose value collected on that night. Summaries of vital signs for PSG nights will be completed using the Safety Population. Observed values and changes from pre-dose will be done by Age Group and overall.

For subjects participating in the PK evaluations, SBP, DBP, pulse rate, respiration rate, body temperature and SpO_2 are obtained prior to dosing on both PK nights. At 1 hour post dose, 4 hours post dose (prior to second nightly Xyrem dosage), 5 hours post dose, and 8 hours post dose, the BP, pulse rate, and respiration rates are collected. SpO_2 is recorded pre-dose and at 1 hour post dose, 2 hours post dose, 4 hours post dose (pre-2nd dose), 5 hours post dose, 6 hours post dose, 8 hours post dose, and while the subject is awake and before release from the study center.

On each PK night, changes will be calculated from the pre-dose value collected on that night. A summary of vital signs on PK night 1 will be completed using the PK Half-Dose Population. A summary of vital signs on PK night 1 and 2 will be completed using the PK Full-Dose Population.

11.6. PHYSICAL STATURE

For Part 1, measurements of physical stature, height (cm) and weight (kg), are completed at each clinic visit during the study. For Part 2, the measurements of physical stature are collected at Visit 17 and Visit 18 (for subjects who re-enrolled after completion of Part 1), and at the quarterly on-site clinic visits.

Body mass index (BMI) will be calculated at each visit as:

BMI = Weight (kg) / (Height $(m)^2$).

Age and sex based percentiles for height, weight, and BMI at each assessment will be determined using the 2000 CDC growth charts published by the Centers for Disease Control (CDC) (Kuczmarski et al, 2002). The CDC has published a SAS program, including reference datasets for determination of these percentiles. The website containing the information with this information is at:

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Percentiles will be based on age in months at the date of the assessment.
Percent change from baseline in weight will be categorized as:

- ≥ 15% decrease
- 10 - < 15% decrease
- 7 - < 10% decrease
- < 7% weight change
- 7 - < 10% increase
- 10 -< 15% increase
- ≥ 15% increase

For Part 1 and Part 2, summaries of observed values, change from Part 1 Day 1 baseline, change from Part 2 Day 1 baseline, and categorized percent changes (Part 1 only) in weight, height, and BMI values and percentiles will be provided for all treatment periods.

Graphical summaries of height, weight, and BMI percentiles will be created separately for Part 1 and Part 2. The graph of the mean values, with bars for +/- 1 SD (or Standard Error as appropriate), will be presented covering all dosing periods, using the Safety Population who Took Study Drug in any period. For the DB Period, means and error bars will be presented separately for those who received Placebo in the DB Period vs. those who received Xyrem in the DB Period. Similar presentations by Age Subgroup and Xyrem Status Subgroup will be presented.

11.7. ECG

During Part 1, ECGs are collected at Visit 1 (Screening), Visit 4 (End of Double-Blind Treatment Period/Beginning of Open-Label Safety Period), and at Visit 15 (Week 52) or ET. The interval measurements and interpretations are being provided by a central reader, Clinilabs. ECGs are not scheduled for collection in Part 2. The reader will provide for each assessment the following assessments:

- Heart Rate (HR) in beats/minute
- RR Interval in msec

- PR Interval in msec
- QRS Interval in msec
- QT Interval in msec
- QTc Bazett's correction (QTcB) in msec
- Overall Interpretation of ECG

Threshold values for the QT and QTcB will be defined as follows:

- QT > 440 msec
- QT > 450 msec
- QT > 480 msec
- QT > 500 msec
- QTcB > 440 msec
- QTcB > 450 msec
- QTcB > 480 msec
- QTcB > 500 msec
- Change from baseline in QT > 30 msec
- Change from baseline in QT > 60 msec
- Change from baseline in QTcB > 30 msec
- Change from baseline in QTcB > 60 msec

In the event of multiple assessments during a period, the worst evaluation will be selected for analysis and highest interval values will be selected for analysis.

Summarizations of Overall Interpretation, QT and QTcB values exceeding the defined thresholds, observed values and change from baseline in ECG intervals will be provided for the Screening, DB, and OL treatment periods.

A shift table comparing Overall Evaluation at Screening vs. the Overall Evaluation at the end of DB Period will be completed. A similar shift table comparing Overall evaluation at Screening vs. Overall Evaluation at the final visit will be completed.

11.8. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is used to measure suicide ideation and behavior. 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. During Part 1, assessments of the C-SSRS are made at each contact with the subject, including phone contacts. The C-SSRS is not scheduled for collection in Part 2. The instruments are presented in full in the protocol document Appendix 8.

The following C-SSRS questions on the scale have binary responses (yes/no).

- Suicidal Ideation (Categories 1 – 5)
    1. Wish to be dead
    2. Non-specific active suicidal thoughts
    3. Active suicidal ideation with any methods (not plan) without intent to act
    4. Active suicidal ideation with some intent to act, without specific plan
    5. Active suicidal ideation with specific plan and intent
- Suicidal Behavior (Categories 6 – 10)
    6. Preparatory acts or behavior
    7. Aborted attempt
    8. Interrupted attempt
    9. Non-fatal suicide attempt
    10. Completed suicide (only collected on "Since Last Visit" version)
- Any Suicidal Ideation or Behavior (1-10)
- Self-injurious Behavior without Suicidal Intent

For each period, the observed Suicidal Ideation, Suicidal Behavior, any Suicidal Ideation or Behavior, and any Self-injurious behavior without suicidal intent will be summarized by visit.

A listing of subjects with any Suicidal Ideation, Suicidal Behavior, or Self-Injurious Behavior without Suicidal Intent will be provided.

11.9. POLYSOMNOGRAPY (PSG)

During Part 1, polysomnography assessments are done during the Screening Period, Visit 3 (End of Stable Dose Period) (for Xyrem Naïve subjects at study entry), and Visit 15 (Week 52) or ET. PSG assessments are not scheduled for collection in Part 2. The data for these assessments will be provided by Clinilabs. The following list of parameters, provided by the vendor Clinilabs, will be summarized. For subjects on Xyrem at entry, the parameters are recorded for the first half of the night, second half of the night, and full night. For Xyrem Naïve subjects, the parameters are provided for the full night at screening and by first half of the night, second half of the night, and full night at subsequent visits.

PSGNAME (Parameter Name)	PSGLABEL (Description)	PSGRESU (Unit)
SOL	Sleep Onset latency	MIN

PSGNAME (Parameter Name)	PSGLABEL (Description)	PSGRESU (Unit)
REML	REM latency	MIN
TNRM	Total NREM	MIN
WASO	Wake after persistent sleep	MIN
REM	Stage R in minutes	MIN
STN1	Stage N1 Sleep in minutes	MIN
STN2	Stage N2 Sleep in minutes	MIN
STN3	Stage N3 Sleep in minutes	MIN
P_REM	Stage R in percentage	%
P_STN1	Stage N1 Sleep in percentage	%
P_STN2	Stage N2 Sleep in percentage	%
P_STN3	Stage N3 Sleep in percentage	%
SaO2_L90	Total time in minutes that SaO_2 is less than 90% during TST	MIN
SaO2_L85	Total time in minutes that SaO_2 is less than or = to 85% during TST	MIN
SaO2_L80	Total time in minutes that SaO_2 is less than 80% during TST	MIN
SaO2_L70	Total time in minutes that SaO_2 is less than 70% during TST	MIN
SaO2_L60	Total time in minutes that SaO_2 is less than 60% during TST	MIN

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PSGNAME (Parameter Name)	PSGLABEL (Description)	PSGRESU (Unit)
SaO2_L50	Total time in minutes that SaO_2 is less than 50% during TST	MIN
SaO2_MN	Mean SaO_2 during TST	%
SaO2_MIN	Minimum oxygen saturation (nadir) during Total Sleep Time	%
SaO2_1hr	Average $SaO_2$1 hr after 1st dose = IPAP 1	%
SaO2_2hr	Average SaO2 2 hrs after 1st dose = IPAP 2	%
SaO2_4hr	Average SaO_2 4 hrs after 1st dose = IPAP 3	%
SaO2_6hr	Average SaO_2 6 hrs after 1st dose = IPAP 4	%
SaO2_8hr	Average SaO_2 8 hrs after 1st dose = IPAP 5	%
EtCo2MX	Highest $EtCO_2$ (study time)	TORR
CA	Number of Central Apnea with onset during Total Sleep Time	NUM
OA	Number of Obstructive Apnea with onset during Total Sleep Time	NUM
A	Number of Apnea with onset during Total Sleep Time	NUM
H	Number of Hypopnea with onset during Total Sleep Time	NUM
CI	Central Apnea Index	NUM/H
OI	Obstructive Index	NUM/H
AI	Apnea Index	NUM/H

PSGNAME (Parameter Name)	PSGLABEL (Description)	PSGRESU (Unit)
OHI	Obstructive Apnea + Hypopnea Index	NUM/H
AHI	Apnea + Hypopnea Index	NUM/H

The percentage of sleep time where the SaO_2 was below 90%, less than or equal to 85%, below 80%, below 70%, below 60%, and below 50% will be derived by dividing the parameters named SaO2_L90, SaO2_L85, SaO2_L80, SaO2_L70, SaO2_L60, and SaO2_L50 by the Total Sleep Time and multiplying by 100%.

A summary of values during the screening period will be completed using the Safety Population.

For Xyrem Naïve subjects, observed values and changes from baseline in the parameters at the end of the SD Period will be completed using the Safety Population who Took Study Drug during the SD Period.

End of study assessments will be summarized for the Safety Population. The summarization of observed values and change from baseline will be done by Xyrem Status at Study Entry, Age Group, and Total for subjects who have an end of study PSG performed at the end of the OL Period. The minimum oxygen saturation (nadir) during the test (PSGNAME = SaO2_MIN) will be summarized by Xyrem dosage level in g/night at the time of each PSG night.

11.10. MASC-10

The Multidimensional Anxiety Scale for Children-10 Item (MASC-10) is a short version of the MASC and produces a score that indicates the severity of anxiety problems. During Part 1, the instrument is completed at each clinic visit, as well as at each phone contact that the site makes with the subject during the study for Xyrem Naïve subjects. The MASC-10 is not being collected during Part 2. A response to each of the 10 questions is provided and scored as follows:

- 0 = never true about me
- 1 = rarely true about me
- 2 = sometimes true about me
- 3 = often true about me

The sum of the 10 scores yields a total raw score, which ranges from 0 to 30. A higher

score is indicative of more risks of anxiety in the subject. The total raw score is then converted to an age-based T-score ranging from 29 to 90 using the chart on the next page. If a response is not provided to one or more of the prompts then, the total raw score and T-score will be missing at the visit. T-scores will be determined using the age in years at each assessment. Subjects who are younger than age 8 will be assigned a T-score using the 8-11 age category.

T-scores will be categorized as:

- < 40 = Below Average
- 40-55 = Average
- 56-60 = Slightly Above Average
- 61-65 = Above Average
- 66-70 = Much Above Average
- > 70 = Very Much Above Average

Statistical Analysis Plan

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:____/____/____ (Month / Day / Year) **School Grade:**_____

MASC–10 Profile

For age groups: Column 1 is for 8–11 year olds, Column 2 is for 12–15 year olds, and Column 3 is for 16–19 year olds

	Females			Males		
T	1	2	3	1	2	3
90	.	.	30	.	.	.
89	.	29	.	30	.	28
88	.	28	29	.	26	.
87	.	.	.	29	.	27
86	.	.	.	.	25	.
85	.	.	28	28	.	26
84	.	27	.	.	24	.
83	.	.	27	27	.	25
82	30	26	.	.	23	.
81	.	.	26	26	.	24
80	29	25	.	.	.	.
79	.	.	25	25	22	23
78	28	24	.	.	.	.
77	.	.	.	24	21	.
76	27	.	24	.	.	22
75	.	23	.	23	20	.
74	26	.	23	.	.	21
73	25	22	.	22	.	.
72	.	.	22	.	19	20
71	24	21	.	21	.	.
70	.	.	21	.	18	19
69	23	20	.	20	.	.
68	.	.	20	.	17	18
67	22	.	.	19	.	.
66	.	19	.	.	.	17
65	21	.	19	18	16	.
64	.	18	.	.	.	16
63	20	.	18	17	15	.
62	.	17	.	.	.	.
61	19	.	17	16	14	15
60	18	16	.	.	.	.
59	.	.	16	15	.	14
58	17	.	.	.	13	.
57	.	15	.	14	.	13
56	16	.	15	.	12	.
55	.	14	.	13	.	12
54	15	.	14	.	11	.
53	.	13	.	12	.	11
52	14	.	13	.	.	.
51	.	12	.	11	10	10
50	13	.	12	.	.	.
49	.	11	.	10	9	9
48	12	.	11	.	.	.
47	.	.	.	9	8	8
46	11	10	.	.	.	.
45	10	.	10	8	.	.
44	.	9	.	.	7	7
43	9	.	9	7	.	.
42	.	8	.	.	6	6
41	8	.	8	6	.	.
40	.	7	.	.	5	5
39	7	.	7	5	.	.
38	.	.	.	.	4	4
37	6	6	6	4	.	.
36	.	.	.	.	.	3
35	5	5	.	3	3	.
34	.	.	5	.	.	2
33	4	4	.	2	2	.
32	3	.	4	.	.	1
31	.	3	.	.	1	.
30	2	.	3	1	.	.
29	<1	<3	<3	<1	<1	<1

Copy circled numbers into the boxes to the left. Then, sum the copied numbers for the MASC–10 Total Score, and circle the Total Score on the profile in the column matching the child's age and gender.

	0	1	2	3	1
	0	1	2	3	2
	0	1	2	3	3
	0	1	2	3	4
	0	1	2	3	5
	0	1	2	3	6
	0	1	2	3	7
	0	1	2	3	8
	0	1	2	3	9
	0	1	2	3	10

MASC–10 Total Score

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In Canada, 3770 Victoria Park Ave., Toronto, ON M2H 3M6, 1-800-268-6011,
1-416-424-1700, Fax 1-416-424-1736. Internationally, +1-416-492-2627.
Fax, +1-416-492-3343 or (888) 540-4484.

In the event of multiple recordings of MASC-10 at an analysis visit, the highest reported T-score at the visit will be utilized in the analysis.

Summaries of observed values and changes from baseline, and categorized T-Scores will be completed for all treatment periods.

A graphical presentation of the mean MASC-10 T-Score, with error bars for +/- 1 SD (or Standard Error), will be presented covering all dosing periods, using the Safety Population who Took Study Drug in any period. For the DB Period and the OL Period, means and error bars will be separated, for those who received Placebo in the DB Period vs. those who took Xyrem. The graphical presentation will be also provided by Age Group and Xyrem status at study entry.

11.11. CDI 2: SR[S]

The Children's Depression Inventory 2nd Edition Self-Report Short Version (CDI 2: SR[S]) is a comprehensive assessment of depression symptoms in youth ages 7 to 17 years. It is designed to assess symptoms in the 2 weeks prior to the assessment. During Part 1, this assessment is done at each contact with the subject, including phone contacts throughout the study conduct during the Dose Titration Period for Xyrem Naïve subjects. The CDI 2 is not scheduled for collection in Part 2.

There are 12 items, each with 3 possible responses. The responses to each item are scored from 0 to 2 so that 0 is the best condition and 2 is the worst condition for the test. The items are scored as follows:

	CDI 2: SR[S] Response Score		
Item	**0**	**1**	**2**
1	I am sad once in a while	I am sad many times	I am sad all the time
2	Things will work out for me O.K	I am not sure if things will work out for me	Nothing will ever work out for me
3	I do most things O.K	I do many things wrong	I do everything wrong
4	I have fun in many things	I have fun in many things	Nothing is fun at all
5	I am important to my family	I am not sure if I am important to my family	My family is better off without me
6	I like myself	I do not like myself	I hate myself
7	I am almost never cranky	I feel cranky many times	I feel cranky all the time
8	I make up my mind about things easily	It is hard to make up my minds about things	I cannot make up my minds about things
9	Doing schoolwork is not a big problem	I have to push myself many times to do my schoolwork	I have to push myself all the time to do my schoolwork

Statistical Analysis Plan

	CDI 2: SR[S] Response Score		
Item	**0**	**1**	**2**
10	I am tired once in a while	I am tired many days	I am tired all the time
11	I eat pretty well	Many days I do not feel like eating	Most days I do not feel like eating
12	I do not feel alone	I feel alone many times	I feel alone all the time

The sum of the responses to the scores for the 12 items ranges from 0-36 will be the total score. This total score is converted to a sex and age-based T-score using the chart below. T-scores will be determined using the age in years at each assessment.

[redacted]

Statistical Analysis Plan

By Maria Kovacs, Ph.D.

CDI 2
SELF-REPORT SHORT
Profile

Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Age: _____ Grade: _____ Sex: Male Female (Circle one) Today's Date: ____/____/____ (Year / Month / Day)

Instructions:

1. Circle the Total Raw Score from the Scoring Page under the appropriate sex and age column.
2. Follow the row across to find the corresponding *T*-score and classification.
3. Transfer the *T*-score to the box on the bottom of the page.

T	Total					*T*
	Females		Classification	Males		
	7–12	13–17		7–12	13–17	
90+	13+	19+	Very Elevated	15+	15+	90+
89						89
88		18		14	14	88
87	12					87
86						86
85		17			13	85
84				13		84
83	11					83
82		16				82
81				12	12	81
80		15				80
79	10					79
78				11	11	78
77		14				77
76						76
75	9					75
74		13		10	10	74
73						73
72		12				72
71	8			9	9	71
70						70
69		11	Elevated			69
68						68
67	7			8	8	67
66		10				66
65						65
64		9	High Average	7	7	64
63	6					63
62						62
61		8		6		61
60	5				6	60
59			Average or Lower			59
58		7				58
57				5	5	57
56	4	6				56
55						55
54				4		54
53		5			4	53
52	3					52
51						51
50		4		3	3	50
49						49
48	2	3				48
47				2		47
46					2	46
45		2				45
44	1			1		44
43		1			1	43
42						42
41						41
≤40	0	0		0	0	≤40

T =

MHS
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The T-score will be used in all analyses. The T-score will have a value from "<= 40" to "90+". In the event of a subject having a T-score of "<= 40", 40 will be used for the numeric summaries. Similarly, if the subject has a T-score of "90+", then a 90 will be used in the numeric summaries.

T-scores will be categorized as:

- ≤ 40 = Low
- 41-59 = Average
- 60-64 = High Average
- 65-69 = Elevated
- ≥ 70 = Very Elevated

In the event of multiple recordings of CDI 2: SR[S] at an analysis visit, the highest reported T-score at the visit will be utilized in the analysis.

Summaries of observed values and changes from baseline, and categorized T-Scores will be completed for all treatment periods.

A graphical presentation of the mean CDI T-Score, with error bars for +/- 1 SD (or Standard Error), will be presented covering all dosing periods, using the Safety Population who Took Study Drug in any period. For the DB Period and OL Period, means and error bars will be separated for those who received Placebo in the DB Period vs. those who received Xyrem. The graphical presentation will also be provided by Age Group and Xyrem status at study entry.

11.12. TANNER STAGE

During Part 1, the assessment of Tanner stage for sexual maturity is assessed at Screening and at Visit 15 (Week 52) or Early Termination. The Tanner Stage is not scheduled for collection during Part 2. For Part 1, a shift table of Tanner stage at Screening vs. End of Study will be completed using the Safety Population. The summarization will be done by Age Group and sex.

11.13. PHYSICAL EXAMINATION

Physical examination data will be presented only in a listing and won't otherwise be summarized.

12. INTERIM ANALYSES

As described in Section 9.1, an interim analysis of the primary outcome was completed after 35 randomized subjects had completed the DB Treatment Period. The analysis was completed by the unblinded INC biostatistician and presented to the DSMB.

13. DSMB

The DSMB will function according to the DSMB charter. Periodic summaries of selected safety endpoints will be provided to the DSMB. Summarizations of DT Period, SD Period, blinded DB period, OL Period, and Part 2 summaries will be provided to representatives of Jazz Pharmaceuticals and the DSMB during their open session. Presentations of the DB Period safety endpoints will be presented by the unblinded [redacted] biostatistician to DSMB members only during the closed session of each meeting.

Analyses to be performed for the DSMB are specified in the DSMB charter.

14. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

- In the study protocol, Section 9.1, it states "PK parameters will be assessed by analysis of variance (ANOVA) models using natural log transformed data." The analysis was to assess dose proportionality of C_{max} and AUC_{0-4}. After further consideration, given the range of potential doses, it was decided that a different method would be used to assess dose proportionality. The method is described in Section 10.2 of the SAP under the dose proportionality section.

- In Protocol Amendment 4, section 9.6.1, it states:

  "However, 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. Since the primary efficacy endpoint was reached and the Double-Blind Randomized treatment is discontinued, the sample size to assess the secondary efficacy endpoints will be reduced. Given the positive primary efficacy results and with the expected treatment benefit of Xyrem on the secondary endpoints based on the adult studies, tiered testing on secondary endpoints will be conducted with a significance level of 0.05, with all tests being one-sided, …".

  After review of change in testing by the FDA, it was decided that all tiered testing of the secondary endpoints will be conducted using two-sided testing.

- Section 9.3 of the protocol states: 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.

  After Amendment 4, the Safety Population who had Study Drug Dispensed in the DB Treatment Period will be used to assess demographics and baseline characteristics, safety and efficacy of subjects who were randomized into Double-Blind Treatment Period, but will further include subjects who were continued on Open-label Xyrem during the DB Treatment Period. Inferential comparisons of demographic and baseline characteristics will be completed using the Randomized Population.

- In section 9.3 of the protocol Amendment 5, the Continued Access Population is defined. In the SAP, this population is called the Safety Population who Took Study Drug in the Part 2 Open-Label Continuation Period.

15. REFERENCE LIST

Benjamini, Y., and Y. Hochberg. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society B 57: 289-300.

Conover, W.J. and Iman, R.L. 1981. Rank Transformation as a Bridge Between Parametric and Nonparametric Statistics. *The American Statistician*, Volume 35 Issue 3 (August 1981), 124-129.

Johns, M.W. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep*, 14(6): 540-545 (1991).

Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. Vital Health Stat 11(246). 2002.

Lan, K.K.G., and Wittes, J. (1988). The B-value: A tool for monitoring data. *Biometrics* 44: 579-585.

16. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA) or higher.

Non-compartmental PK parameters, i.e. C_{max}, T_{max}, AUC_{0-4}, $AUC_{0-infinity}$, Half-life, will be calculated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA) or higher.

16.1. GENERAL CONSIDERATIONS

- One SAS program may create several outputs.
- Each output will be stored in a separate file.
- Individual output files will be delivered in RTF format. Combined outputs will be delivered in PDF format.
- Numbering of tables, figures, and listings (TFLs) will follow ICH E3 guidance.

16.2. TABLE, LISTING, AND FIGURE FORMAT

16.2.1. General

- All TLFs will be produced in landscape format.
- All TLFs will be produced using the Courier New font, size 8.

  The data displays for all TLFs will be produced on a landscape oriented page with the following margins specified in inches: Top 1.6”, Bottom, 1.15”, Left 1”, Right 1”.

- Headers and footers for figures will be in Courier New font, size 8.

- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- Tables and Listings will be in black and white; Colors may be used for figures to aid interpretation.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters may be used, where possible, if they

are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) may be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers and Footers

- All output should have the following header at the top left of each page:
  Jazz Pharmaceuticals
  Protocol 13-005
- All output should have Page n of N at the top right corner of each page. TLFs will be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date of output generation should appear along with program name and output name as the last footer on each page.

16.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The study Period of analysis will be included in the title. The title will be centered. The analysis population will be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Population

16.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable).

- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group or category in the column heading as (N=xxx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set with a value for the variable being analyzed.
- For the DT Period tables, the columns for presentation of summaries will include: Age Group 7-11, Age Group 12-17, and Total.
- For the SD Period, the columns for presentation will include: Age Group 7-11, Age Group 12-17, Xyrem Naïve, On Xyrem at Entry, and Total.
- For the DB Period presentations of efficacy endpoints for subjects randomized prior to the implementation of Amendment 4, the columns for presentation will include: Placebo, Xyrem, and Total.
- For the DB Period presentations of efficacy endpoints for subjects entering the period after the implementation of Amendment 4, the columns for presentation will include: Age Group 7-11, Age Group 12-17, Xyrem Naive, On Xyrem at Entry, and Total Open-Label Xyrem.
- For DB Period presentations of safety endpoints, the columns for presentation will include: Randomized to Placebo, Randomized to Xyrem, OL Xyrem, All Xyrem, and Total.
- For the OL Period, in general the columns for presentation will include: Age Group 7-11, Age Group 12-17, Xyrem Naïve, On Xyrem at Entry, and Total. For efficacy parameters collected in the OL Period, the columns for presentation will include: Age Group 7-11, Age Group 12-17, Xyrem Naïve, On Xyrem at Entry, Received Placebo during DB, Received Xyrem during DB, and Total.
- For the OL Continuation Period, the columns for presentation will include: Age Group 7-11, Age 12-17, and Total. When presenting results across Part 1 and Part2, the columns for presentation will include: Age Group 7-11, Age Group 12-17, Xyrem Naïve, On Xyrem at Entry, and Total.

16.2.5. Body of the Data Display

16.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified;

16.2.5.2. Table Conventions

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category will be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
Severe	0
Moderate	8
Mild	3

- Percentage values should be rounded and presented to one decimal place (including 100.0%). Percentages will be presented in parentheses, one space after the count (e.g., 7 (12.8), 13 (5.4), 100 (100.0)). Unless otherwise noted, percentages will be calculated using the number of subjects in the analysis set as the denominator.
- If the categories for a categorical variable are not ordered (e.g., Medical History, Adverse Events, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- Unless otherwise specified, the estimated mean, median, 1st quartile, and 3rd quartile for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations or standard error should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	XXX.XX
Median	XXX.X
Q1	XXX.X
Q3	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999.
- Tabular display of data for prior / concomitant medications, and adverse event data should be presented ordered alphabetically by the class variable (ATC4 level or SOC). Within the class or SOC, drugs or adverse event terms will be presented in descending order by preferred name or preferred term. If the incidence is the same for 2 or more terms, terms will be sorted alphabetically within that incidence level.

- Any percentage calculated using a denominator other than the analysis set population count will be documented on the table using a footnote.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote will be added to indicate that subjects may be counted in more than 1 category.

16.2.5.3. Listing Conventions

- Listings will be sorted in order of Xyrem Status at Study Entry, randomized treatment (or not randomized), country, subject identifier, period of collection, visit number, date and study day of collection.
- Dates should be printed in Year/Month/Day format ("YYYY-MM-DD": 2015-01-25). Missing portions of dates will be represented by blanks.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

16.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis. Going forward all figures will indicate the number of observations available at the study visit.
- By-subject plots of PK concentrations will identify the subject identifier, age, sex, body weight, Xyrem dosage level in g/night. Separate lines will be produced on the page for each PK night. Y axes will always initiate at 0. Nominal elapsed times from first dosing on the PK night will be used.

16.2.5.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or [1], [2], '[3], etc. if a reference footnote. Each new footnote should start on a new line where possible.

- Footnotes provided on the table, listing and figure shells will be, in general, presented on each page of the output. Subject specific footnotes will not be used.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and the date the program was run.

17. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS programs.

[redacted] SOP 03.009.00 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

Each provided analysis dataset (i.e. CDISC ADaM), output table, and output listing will be checked for accuracy using double programming. An independent programmer or biostatistician will reprogram the results and compare using the SAS procedure PROC COMPARE. Values and order of presentation will be compared. The outputs will be compared to the table, listing, and figure shells for accuracy. The quality control of figures will be achieved using a comparison of figure results to already created summarization tables or with double-programming.

18. INDEX OF TABLES

The index of tables will be provided in a separate document.

19. INDEX OF FIGURES

The index of figures will be provided in a separate document.

20. INDEX OF LISTINGS

The index of listings will be provided in a separate document.

21. MOCK-UPS

21.1. TABLE MOCK-UPS

Table mockups will be provided in a separate document.

21.2. FIGURE MOCK-UPS

Figure mockups will be provided in a separate document.

A detailed description of the figure may be used in lieu of a figure template. Here is an example:

Figures 14.4.1.4: Mean Plasma Concentration Over Time by Treatment Group (PK Analysis Set)

PROGRAMMING NOTES:

- This figure is a line plot and corresponds to Data Listing XXXXX Drug Concentration Data.
- Axes: Vertical axis: Mean plasma drug concentration (units),. Include vertical axes on both the left and right sides of the figure. Horizontal axis: Nominal time Post-Dose (hours), with range from 0 hour (pre-dose) to X hours post-dose.
- Solid lines should connect the data points for the means. One line per treatment group will be plotted.
- Solid circles will be used for mean values in treatment group X; triangles will be used for mean values in treatment group Y. Include a legend that indicates which treatment group a circle represents and which treatment group a triangle represents.
- Error bars should be used at each visit that represents standard deviations.
- Include the number of subjects with data at each time point below the horizontal axis.
- Include footnote “Values below limit of quantification were imputed to xxxxx.”
- The [redacted] stamp (program name, date, etc.) should appear at the bottom of the figure.

21.3. LISTING MOCK-UPS

Listing mockups are provided in a separate document.

22. APPENDICES

Not applicable.