Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (S-030)**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Drug:	**Xyrem**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Supplemental New Drug Application**
Correspondence Date:	**4/27/18**
Date Received By Reviewer:	**4/30/18**
Date Review Completed	**10/26/18**
Reviewer:	**Ranjit B. Mani, M.D.**

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Executive Summary

Recommendation

I recommend that this application be approved.

Proposed Indications

The proposed indications for Xyrem®, as stated by the sponsor in the original submission of this application, are as follows:

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy in adult and pediatric patients."

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness in narcolepsy in adult and pediatric patients."

Currently Approved Indications

The currently approved indications for Xyrem® are as follows:

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy."

"Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness in narcolepsy."

Background To Application

This Supplemental New Drug Application (sNDA), a pediatric efficacy supplement, seeks to expand the approved indication for Xyrem® (sodium oxybate) to include the treatment of children. A priority review of this supplement has been requested and granted. This application is accompanied by a Pediatric Exclusivity Request.

The clinical data subsumed under this application have been submitted in response to a pediatric Written Request from the Agency initially issued on March 10, 2014, and subsequently modified; the Request was finalized on April 25, 2017.

Xyrem® (sodium oxybate oral solution [500 mg/mL]) is currently approved in this country for the treatment of cataplexy and excessive daytime in narcolepsy. Xyrem® was initially approved for marketing in the United States on July 17, 2002. The original approval of Xyrem® was under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® was originally approved for marketing under a restricted distribution program. A formal Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® was approved on February 27, 2015.

Most of the new clinical data that are submitted with this application are derived from the results of Study 13-005, a clinical study conducted in response to the pediatric Written Request.

Summary of Main Clinical Findings

Study 13-005 is the main clinical study supporting this sNDA. Key aspects of this study are summarized below.

Study Design And Significant Amendments

Protocol 13-005 had the following main features:

- The primary objectives of the study were to evaluate the efficacy and safety of Xyrem® in the treatment of pediatric patients (aged 7 to 17 years) who have narcolepsy with cataplexy

- This study had a number of consecutive segments, of which the main randomized, double-blind, placebo-controlled, parallel-arm withdrawal segment was to be the component of the study directed at evaluating the efficacy of Xyrem® in the treatment of cataplexy associated with narcolepsy in children.

- About 100 patients aged 7 to 16 years at study entry were to be enrolled. They would be either Xyrem®-naïve or taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry. Other key inclusion criteria were as follows: primary diagnosis of narcolepsy with cataplexy meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study; positive for the HLA DQB1:0602 haplotype; and history of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Throughout the study, all nightly doses of Xyrem® and placebo were to be administered in 2 divided doses, administered 2.5 to 4 hours apart. The starting and maximum doses of Xyrem® as well as the Xyrem® titration regimen (if required) were to be determined based on body weight stratum.

- The consecutive segments of this study were as follows:

    - A screening period lasting up to 30 days.

    - A 3 to 10 week open-label titration period lasting 3 to 10 weeks for patients who were Xyrem®-naïve at study entry.

    - An open-label stable-dose period lasting 2 to 3 weeks. During this phase, a subset of about 24 patients (completers) who were taking a stable dose of Xyrem® at study entry were to participate in an open-label evaluation of the pharmacokinetics of Xyrem®.

    - A double-blind, placebo-controlled withdrawal phase lasting 2 weeks during which period patients were randomized 1:1 to treatment either with Xyrem® in the stable dose established during the preceding 2 weeks or placebo.

    - An open-label safety component which allowed for a total exposure to Xyrem® of up to 1 year.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

- Key secondary efficacy parameters were the following:

    - Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in the modified Epworth Sleepiness Scale (modified for children and adolescents) score from the end of the stable-dose period to the end of the double-blind period.

- Other secondary efficacy parameters were the following

    - Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

- Safety monitoring was to comprise assessment of the following during the course of the study: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests, assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index.

- Plasma concentrations of sodium oxybate were measured in the subset of patients participating in the pharmacokinetic analysis, and various pharmacokinetic parameters derived from those data and analyzed further.

- A tiered analysis of the efficacy parameters was conducted beginning with the primary efficacy parameter followed by the two key secondary efficacy parameters (with the Clinical Global Impression of Change in cataplexy severity analyzed first and the change in modified Epworth Sleepiness Scale score analyzed later), and finally the two other secondary efficacy parameters in the same order as stated above.

A pre-specified interim efficacy analysis (on the primary efficacy endpoint) for this protocol that was conducted after 35 subjects completed or discontinued early from the double-blind treatment period led to the Data Safety Monitoring Board for Study 13-005 concluding that Xyrem had demonstrated efficacy in the treatment of cataplexy (it had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value ≤ 0.005): the Board then recommended that the double-blind segment of Study 13-005 be discontinued, while the open-label extension (including pharmacokinetic evaluation) continue. The Data Safety Monitoring Board for Study 13-005 also

recommended that patients continue to be enrolled in the open-label pharmacokinetic segment.

The pediatric Written Request under which Study 13-005 was first conducted was amended after the pre-specified interim analysis led to a protocol amendment. The study protocol was also amended to allow for the duration of the open-label safety component to be further extended so that the total duration of Xyrem® treatment for an individual patient could extend up to 3 years; the part of the study originally proposed was then referred to as Part 1 with the newly-proposed extension as Part 2.

Study Results

Study 13-005 was conducted in a manner consistent with the study protocol.

A total of 106 patients were enrolled in this study of whom 104 appear to have received study drug. 99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem. 95 patients then entered the open-label safety period of the study. As of the cut-off date for the 120-day safety update, 85 patients had completed Part 1 of the study and 44 patients had entered Part 2.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two -week randomized withdrawal period in the weekly number of cataplexy attacks was 17.37 for the placebo group and 2.52 for the group that continued to take Xyrem® (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring Xyrem® over placebo were seen on the two key secondary efficacy parameters analyzed in the prespecified sequence, the Clinical Global Impression of Change for Cataplexy Severity ($p = 0.0006$) and the change from baseline in modified Epworth Sleepiness Scale score ($p = 0.0001$).

The adverse event profile of Xyrem® seen in this study was not substantially different from that seen in adults. The other safety outcomes did not reveal any data of concern. Safety data for this study that was submitted with the 120-Day Safety Update was not substantially different from that submitted with the original IND for Xyrem®.

The pharmacokinetic completer population consisted of 29 patients, of whom 11 were aged 7 to 11 years, and 18 were aged 12 to 17 years. These data revealed a pharmacokinetic profile for Xyrem® in children that was similar to that seen in adults. A dose-proportionality assessment indicated that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

Additional Clinical Findings

Additional safety data for children administered Xyrem® was provided from two sources: postmarketing safety data for Xyrem® comprising data collected since the original approval for Xyrem®; and the published medical literature. The data available indicate a safety profile that is broadly similar to that seen in adults.

Proposed Changes To Labeling

These are described in more detail in the body of this review.

Additional Comments

Study 13-005 has been conducted in accordance with the terms of the pediatric Written Request finalized on April 25, 2017.

The reviews by a number of other Agency staff are also summarized in the body of this review.

Conclusion

This Supplemental New Drug Application has provided sufficient data to support the approval of Xyrem® for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy, in pediatric patients aged 7 years and older.

1. Background

This Supplemental New Drug Application (sNDA), a pediatric efficacy supplement, seeks to expand the approved indication for Xyrem® (sodium oxybate) to include the treatment of children.

This sNDA is also accompanied by a Pediatric Exclusivity Request. A priority review of this supplement has been requested and granted.

Xyrem® (sodium oxybate oral solution [500 mg/mL]) is currently approved in this country for the treatment of cataplexy and excessive daytime in narcolepsy. Xyrem® was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A supplemental NDA (an efficacy supplement; S-005) proposing an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication was (and still is) as follows: "*The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy*." Xyrem® was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® was originally approved for marketing under a restricted distribution program. A formal Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® was approved on February 27, 2015.

The development of Xyrem® as a treatment for cataplexy in children (i.e., children and adolescents, aged 7 to 17 years) was conducted in response to a pediatric Written Request, initially issued by the Agency on March 10, 2014. After the results of an interim (efficacy) analysis of the double-blind segment of the main study (Study 13-005) conducted under that Written Request became available, an amended Pediatric Written Request was issued by the Agency on February 24, 2017; a few corrections were made to the amended Written Request in a final document issued by the Agency on April 25, 2017.

The clinical data included in this application are largely derived from Study 13-005.

There have been many communications between the Agency and sponsor regarding the development of Xyrem® for use in children, culminating in a Pre-sNDA meeting held on September 6, 2017.

Xyrem® has been investigated for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in children under IND 49641.

2. Contents Of Submission

This sNDA submission has two main components.

- The original sNDA submission of April 27, 2018, which has been provided in standard electronic Common Technical Document format. This component has five main sections, enumerated and headed as follows:

  Module 1: Regional.
  Module 2: Common Technical Document summaries.
  Module 3. Quality.
  Module 4. Nonclinical study reports.
  Module 5. Clinical study reports.

- A 120-Day Clinical Safety Update submitted on August 23, 2018, which has also been provided in standard electronic Common Technical Document format. This component thus has three main sections, enumerated and headed as follows:

  Module 1: Regional.
  Module 2: Common Technical Document summaries.
  Module 5. Clinical study reports.

Since the original submission of this sNDA, there have a number of additional communications such as, but not limited to, information requests and responses to those requests from the sponsor.

3. Contents Of Review

The contents of this submission have been reviewed under the following main headings and in the same order as below.

- Final text of pediatric Written Request.
- Pre-sNDA meeting.
- Outline of main clinical study (Study 13-005) supporting current application.
- 120-Day Safety Update.
- Additional safety data supporting current application.
- Review of proposed Prescribing Information and related documents.
- Summary of statistical review.
- Summary of nonclinical review.
- Summary of clinical pharmacology review.
- Summary of chemistry review.
- Summary of Office of Surveillance and Epidemiology reviews.
- Summary of Office of Prescription Drug Promotion (OPDP) reviews
- Controlled Substances Staff review.
- Financial disclosure information.
- Site inspection report.
- Fulfilment of terms of pediatric Written Request.
- Overall conclusion.
- Recommendation.

Note that the following are subsumed under this review: primary clinical review, and team leader and cross-disciplinary team leader summary.

4. Final Text Of Pediatric Written Request

The following is the full text of the Amended Written Request that was sent to the sponsor on April 25, 2017. The text is copied verbatim from the letter but has been re-formatted.

Please refer to your correspondence dated October 25, 2016, requesting changes to FDA's March 10, 2014 Written Request for pediatric studies for Xyrem (sodium oxybate) oral solution.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 10, 2014 remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

This Written Request has been amended as a result of an interim analysis of Study 1, described below. The independent Data Safety Monitoring Board conducted a prospectively planned analysis after 35 patients had either completed or discontinued the double-blind segment of that study. The Board reached the conclusion that there were adequate data to support the efficacy of Xyrem in the treatment of cataplexy in children and adolescents aged 7 to 17 years. They recommended: that the double-blind segment of the study be discontinued; that the open-label safety segment of that study be continued; and that patients continue to be enrolled in the open-label pharmacokinetic segment of the study.

This study plan investigates the potential use of sodium oxybate oral solution in the treatment of cataplexy in narcolepsy in children and adolescents aged 7 to 17 years.

Narcolepsy is a lifelong neurological disease estimated to be prevalent in 0.02% of adults worldwide, and in about 1 in 2000 individuals in the United States. The cardinal symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, sleep-related hallucinations, sleep paralysis, and disrupted nighttime sleep. The age of onset of narcolepsy ranges from early childhood to middle age, with a large peak around age 15: thus the first symptoms of narcolepsy commonly manifest during childhood and adolescence.

Cataplexy is a symptom specific to narcolepsy and is characterized by a sudden loss of skeletal muscle tone often triggered by strong emotions such as laughter. The loss of muscle tone in cataplexy may be confined to a limited group of muscles or be more generalized. Localized forms of cataplexy may manifest with symptoms such as head or jaw dropping, buckling of the knees, and slurred speech. Generalized cataplexy with a loss of tone in all voluntary muscles can result in falls. The duration of individual attacks of cataplexy can vary from a second to several minutes. The frequency of attacks of cataplexy can vary from as little as one episode per year to several episodes per day, with attacks occasionally being continual for several hours at a time. Consciousness is fully preserved during attacks of cataplexy. The prevalence of cataplexy in the United States has been estimated to range from 0.05% to 0.067%. Like other symptoms of narcolepsy, cataplexy commonly begins during childhood and adolescence.

As is the case with adults, the symptoms of narcolepsy, including cataplexy, are frequently disruptive of the lives of children and adolescents, both at school and elsewhere. Among several consequences of narcolepsy in that population are impaired academic performance, injury, and emotional disturbances.

Sodium oxybate is the only drug approved for the treatment of cataplexy in narcolepsy. The approval of sodium oxybate for the treatment of cataplexy in narcolepsy is based on studies conducted entirely in adults, as is the approval of that drug for the treatment of excessive daytime sleepiness in narcolepsy. While other drugs such as tricyclics and selective serotonin reuptake inhibitors are used in both adults and children to treat cataplexy, their use for that indication is not evidence-based. Stimulant drugs such as methylphenidate and dextroamphetamine, while prescribed for the treatment of the excessive daytime sleepiness of narcolepsy even in children, are not approved for use in that population and are not known to be effective in cataplexy.

Section 8.4 of the current Prescribing Information for sodium oxybate states the following: "*Safety and effectiveness in pediatric patients has not been established.*" There are also no published randomized, controlled trials of sodium oxybate in pediatric patients. Despite similarities in the symptoms of narcolepsy between children and adults, we do not believe that sodium oxybate can be assumed to have efficacy in children and adolescents based on the extrapolation of efficacy data from adults. There are, however, post-marketing safety data available for about 1500 pediatric patients who were prescribed sodium oxybate off-label.

For the above reasons, the potential use of sodium oxybate as a treatment for cataplexy in narcolepsy in children and adolescents aged 7 to 17 years should be clinically investigated. Narcolepsy is less frequent in children less than 7 years old and has not been reported to occur in neonates; thus, the potential use of sodium oxybate in those populations does not warrant further investigation.

To obtain needed pediatric information on sodium oxybate the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study*:

Based on review of the available nonclinical toxicology data, the following study must be conducted, but may be conducted concurrently with the clinical study in pediatric patients further described below:

A juvenile animal toxicology study in rats.

This study must utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals must be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects on growth (including bone growth parameters), reproductive development, and neurological and neurobehavioral development. Reproductive performance must be evaluated following cessation of treatment, after a washout period of appropriate duration (based on half-life). In assessing neurobehavioral development, the effects must be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals must be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests must assess sensory function, motor function, and learning and memory. The neuropathological evaluation must include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

We recommend that dose selection for the pivotal study be based on a preliminary dose-range finding study in juvenile animals, and that a final protocol for the pivotal nonclinical study be submitted to the Division for comment prior to study initiation.

- *Clinical study:*

Study 1: A double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of sodium oxybate, combined with an open-label evaluation of the pharmacokinetics of sodium oxybate, and an open-label safety evaluation with combined time of sodium oxybate treatment of at least one year in pediatric patients who have narcolepsy with cataplexy.

The efficacy of sodium oxybate in pediatric patients aged 7 to 17 years cannot be extrapolated and will be determined by the studies outlined in this Written Request.

- *Objectives of the study:*

- to evaluate the efficacy of sodium oxybate in the treatment of cataplexy in narcolepsy in pediatric patients aged 7 to 17 years
- to evaluate the safety of sodium oxybate in the treatment of cataplexy in pediatric patients, aged 7 to 17 years, for at least one year.
- to characterize the pharmacokinetics of sodium oxybate given as two doses to children and adolescents, aged 7 to 17 years, who have narcolepsy with cataplexy.
- to compare the pharmacokinetics and dose-proportionality of sodium oxybate in two pediatric age group distributions (7-11 years and 12-17 years), and to further compare those data with corresponding historic data for sodium oxybate in adults.

- *Patients to be Studied:*

- *Age group in which study will be performed*: Patients aged 7 to 17 years.

- *Number of patients to be studied:* At least 100 patients should be enrolled in the study as a whole. At least 8 patients from the 7-11 year age group distribution and 10 patients from the 12-17 year age group distribution should be enrolled in the subset of subjects in whom pharmacokinetic analyses are to be performed.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

- Efficacy Endpoints: The primary efficacy endpoint will be the change in the weekly number of cataplexy attacks during the 2 weeks of double-blind treatment as compared with the weekly number of cataplexy attacks during the 2-week (stable-dose) period immediately preceding the double-blind treatment period.

A key secondary efficacy endpoint must be the Clinical Global Impression of Change in cataplexy severity comparing the end of the double-blind period with the end of the stable- dose period.

Measures of compliance must include measurement of the volume of sodium oxybate remaining at each study visit in each bottle in which that product is dispensed.

- Pharmacokinetic Endpoints: The following pharmacokinetic parameters for sodium oxybate must be evaluated in a subset of patients who are already taking sodium oxybate at a stable dose: AUC0-4, Cmax, and tmax following the first dose; and peak concentration and C4h after the second

dose. Those pharmacokinetic parameters and the dose-proportionality of sodium oxybate in each of the two pediatric age group distributions (7-11 years and 12-17 years) must be assessed and compared with the corresponding historic data in adults.

- Safety Endpoints: Safety outcomes must include an evaluation of adverse events, vital signs, physical examinations, weight, height, 12-lead electrocardiogram, hematology, clinical chemistry, urinalysis, polysomnographic measures (including measures of respiration), assessments of growth and precocious puberty (including measurement of growth hormone), serum pregnancy tests (if appropriate), Columbia-Suicide Severity Rating Scale score, Children's Depression Inventory score, and Multidimensional Anxiety Scale score.

A review of adverse events must be performed at every study visit. Vital signs, height, and weight should also be checked at every study visit using standardized methods. Other assessments should be performed at clinically appropriate intervals, again using standardized methods.

While all adverse events must be reported, patients must be actively monitored for the following adverse events: confusion, somnolence and more pronounced levels of depressed consciousness; respiratory depression; depressed mood and suicidality; anxiety; sleepwalking and other parasomnias; abuse and misuse of sodium oxybate; and weight loss.

A Data Monitoring Committee must be included because of the known safety concerns with sodium oxybate that are listed below. Please refer to the Agency Guidance document entitled "Establishment and Operation of Clinical Trial Data Monitoring Committees" which is available at the following link.

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Known Drug Safety concerns and monitoring:*

Known safety concerns with sodium oxybate include central nervous system depression, respiratory depression, confusion, depressed mood and suicidality, anxiety, parasomnias such as sleepwalking, and abuse and misuse of that drug. The current Prescribing Information for sodium oxybate especially warns of the risk of respiratory and central nervous system depression, and misuse and abuse of that product. Accordingly, patients should be actively monitored for those adverse events. The use of sodium oxybate is contraindicated in combination with sedative hypnotics or alcohol and in individuals with succinic semialdehyde dehydrogenase deficiency. Sodium oxybate is a Schedule III controlled substance and sodium oxybate is available only through a restricted distribution program because of the risks of central nervous system depression, abuse, and misuse.

- *Extraordinary results:*

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form: liquid*
  - *route of administration: oral*
  - *regimen: nightly in two divided doses*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if
1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,
the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

The trial must enroll a sufficient number of patients to have at least 80% power to detect a difference between the two treatment groups of 40% in the percentage change in the weekly number of cataplexy attacks during the 2-week randomized withdrawal phase of the study as compared with the 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. A hypothetical example of such a difference between the treatment groups is illustrated in the following table.

Treatment Group	**Weekly number of attacks during last 2 weeks of stable dose**	**Weekly number of attacks during 2-week randomized withdrawal period**	**Change in weekly number of attacks**	**% change in weekly number of attacks***	**Difference between treatment groups in**
Placebo	10	15	5	+50%	40%
Xyrem	10	11	1	+10%	

*compared with last 2 weeks of stable-dose period
**effect size

Dose proportionality must be assessed using AUC and Cmax values. The AUC and Cmax ratios and their 90% confidence intervals should be presented. Pharmacokinetic parameters will be based on the PK population available.

- *Labeling that may result from the study(ies)*:

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that sodium oxybate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*:

You must submit full study reports, not previously submitted to the Agency, that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):*

Reports of the above studies must be submitted to the Agency on or before September 22, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:*

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Reports of the studies that meet the terms of the Written Request dated March 10, 2014, as amended by this letter must be submitted to the Agency on or before September 22, 2018 in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission , via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written

5. Pre-sNDA Meeting

A Pre-sNDA meeting was held with the sponsor on September 6, 2017, at which this then-pending application was discussed. For full details of the items discussed and agreements reached at that meeting, please see the Agency's Minutes.

6. Outline Of Main Clinical Study (Study 13-005) Supporting Current Application

6.1 Outline Of Study Protocol Through Amendment #3

The outline below summarizes the main features of this study protocol as it existed prior to the conduct of an interim analysis described below.

The protocol described below is the version contained in Amendment #3, dated August 5, 2015, which was submitted to IND #49641 on August 11, 2015 (Serial #246). Substantive changes to the protocol were made in Amendment #s 4 and 5 and are summarized later in this review.

Please note that the citations in sponsor tables copied below refer to the items in the study protocol submitted by the sponsor.

6.1.1 Title

A Double-Blind, Placebo-Controlled, Randomized-Withdrawal Multicenter Study Of The Efficacy And Safety Of Xyrem With An Open-Label Pharmacokinetic Evaluation And Safety Extension In Pediatric Subjects With Narcolepsy With Cataplexy.

6.1.2 Objectives

6.1.2.1 Primary Objectives

- To evaluate the efficacy of Xyrem® in the treatment of cataplexy in pediatric patients with narcolepsy.
- To evaluate the safety of Xyrem® in the treatment of cataplexy in pediatric patients with narcolepsy for up to one year.

6.1.2.2 Secondary Objectives

- To evaluate the efficacy of Xyrem® in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy with cataplexy.
- To characterize the pharmacokinetics of Xyrem® in pediatric patients, aged 7 to 17 years, with narcolepsy with cataplexy.
- To evaluate the safety of titrating Xyrem® in pediatric patients to an effective and tolerable dose.

6.1.3 Design, Dose, Sample Size, And Duration

This study consists of 2 consecutive core components.

1. The key double-blind, placebo-controlled, randomized withdrawal component of the study (with the double-blind, placebo-controlled randomized withdrawal segment forming a phase in that component of the study).

2. An open-label safety extension, following the period of double-blind withdrawal that permits all patients to receive Xyrem® for a total period of up to 1 year.

Patients to be enrolled in the study will be either Xyrem®-naïve or already taking that drug.

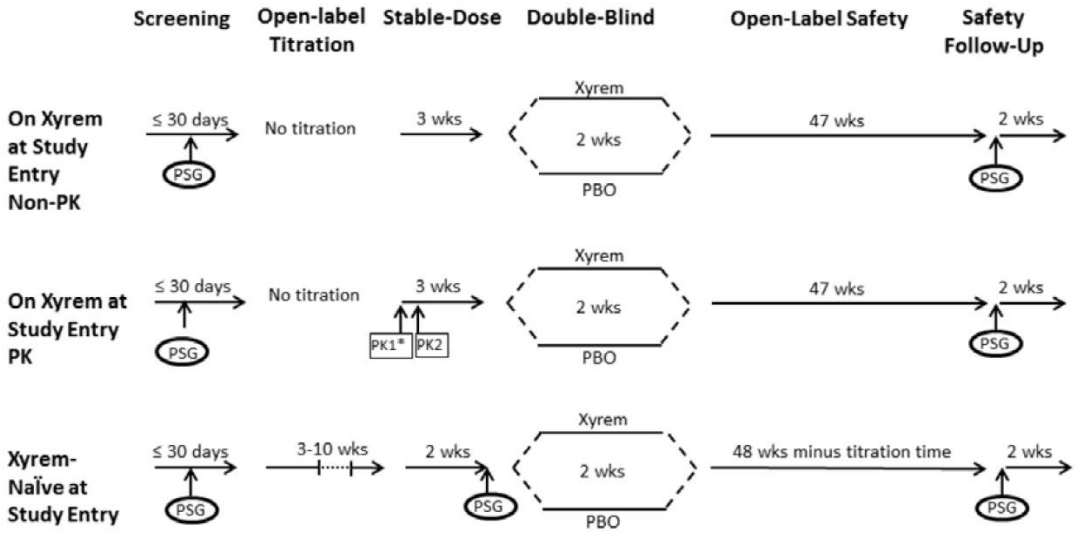
Open-label titration and open-label stable dose periods, in that consecutive order, are to precede the double-blind, placebo-controlled, randomized withdrawal component.

The pharmacokinetics of Xyrem® are to be evaluated in a subset of patients during the first component of the study during the stable-dose period.

Throughout the study, all nightly doses of Xyrem® and (Xyrem®) placebo will be administered in 2 divided doses, administered 2.5 to 4 hours apart.

The Xyrem® product used will be the marketed product, but flavorant may be added to the water used as a diluent if requested by the subject, parent, or guardian for palatability.

The overall study schema is illustrated below in a figure that I have copied from the submission.

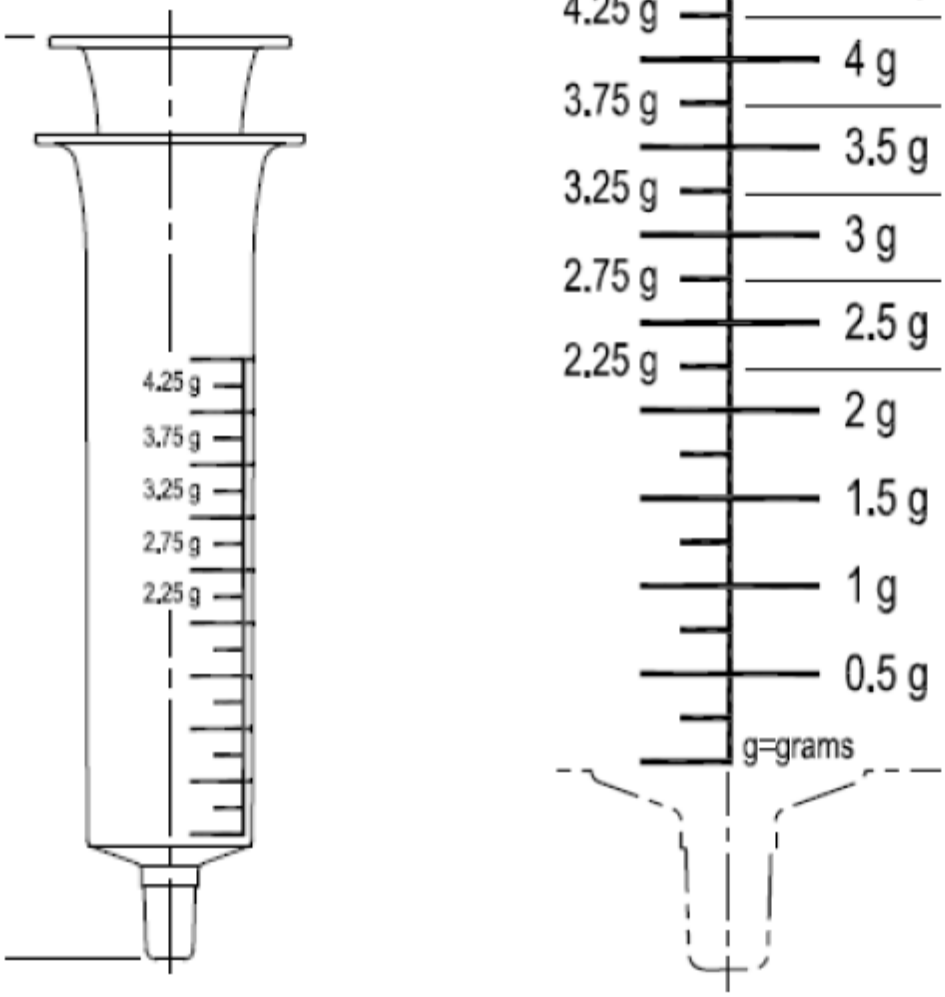


* ½ of usual nightly dose

PK: Pharmacokinetics
PSG: Polysomnogram

Each segment of the study is further described below.

A specific dosing syringe is to be used during the study. An image of that syringe and its gradations is displayed below.



6.1.3.1 Double-Blind, Placebo-Controlled, Randomized Withdrawal Component

The study will have a screening period lasting up to 30 days.

About 100 patients are to be enrolled in the study. Those enrolled will be:

EITHER

- Xyrem®-naïve.

OR

- Taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry.

There will be an open-label titration period lasting 3 to 10 weeks for patients who are Xyrem®-naïve at entry. Those patients will have treatment with that drug initiated at a dose that is weight-dependent. The Xyrem® dose will then be titrated until there is maximum benefit in the treatment of cataplexy (and so that the frequency and severity of cataplexy are stable with no further dose adjustments needed) and excessive daytime sleepiness, while tolerability is maintained. Once an optimal dose of Xyrem® is achieved (per the investigator's judgment), patients may enter the open-label stable-dose period of the study. Patients in whom there is no response based on cataplexy frequency compared with study entry will be considered treatment failures and withdrawn from the study. The starting dose, rate of titration, and maximum dose for Xyrem® for the dose titration phase – all of which are weight-dependent – are specified in the following table, which I have copied from the submission.

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 or 1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later.
**Titration of 1 g/night/week up to 7 g/night and then 0.5 g/night/week final titration permitted.

A reduction in Xyrem® dose on account of poor tolerability will be permitted during the dose-titration phase with any decrement being a multiple of either 1 g/night or 1.5 g/night. Stimulant taper and withdrawal may also be attempted at the discretion of the investigator during the open-label titration phase.

An open-label stable-dose period lasting 2-3 weeks will precede the double-blind, placebo-controlled, randomized withdrawal phase of the study, as follows:

- For patients already taking a stable dose of Xyrem® (and stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry, treatment with the same dose of Xyrem® (and stimulants, if applicable) will be continued for 3 weeks.

- For Xyrem®-naïve patients who have been titrated to an optimal Xyrem® dose (and stimulant dose, if applicable) during the dose-titration phase will remain on the same dose of Xyrem® (and stimulants, if applicable) for 2 weeks during the open-label, stable dose period.

Baseline data will be collected during the last 2 weeks of the stable-dose period.

At the end of the open-label, stable-dose period, patients will be qualified to enter the double-blind treatment period if the following criteria are satisfied:

- Inclusion and exclusion criteria for the study protocol continue to be met.
- The dose of Xyrem® remains unchanged during the stable-dose period.
- No clinically significant worsening in narcolepsy symptoms or clinically significant adverse events attributable to Xyrem® treatment during the stable-dose period as per investigator judgment.

The double-blind, placebo-controlled, randomized withdrawal phase will immediately follow the stable-dose period. This period will last 2 weeks. During this period, patients will be randomized 1:1 to treatment with one of the following regimens:

- Xyrem® continued in the stable dose established during the preceding 2 weeks.
- Placebo that is equivalent in volume to the Xyrem® stable dose established during the preceding 2 weeks.

During the double-blind, placebo-controlled, randomized withdrawal period, patients will remain on the same stimulant dose (if applicable) that was used during the open-label stable-dose period.

Patients who complete the double-blind treatment period will be eligible to continue in the open-label safety component of the study.

During the **open-label stable-dose** phase described above, a subset of patients will participate in the open-label pharmacokinetic evaluation further described below.

6.1.3.1.1 Open-Label Pharmacokinetic Evaluation

Only patients already taking a stable dose of Xyrem® at study entry will be eligible to participate in the pharmacokinetic evaluation section of the study.

Patients enrolled will be stratified into 2 groups by age: 7 to 11 years; and 12 to 17 years. If the variability of Xyrem® pharmacokinetics in children is similar to that in adults, 12 completers in each age group are estimated to be adequate to characterize the pharmacokinetics of Xyrem® in children. When sufficient data are actually available to characterize the pharmacokinetics of Xyrem® in children, enrollment in that component of the study will cease.

Once enrolled in the pharmacokinetic evaluation, patients will spend two nights at the beginning of the stable-dose period (or during the earlier open-label stable dose period) at the study site for the pharmacokinetic evaluation. These two nights are designated (in consecutive order) as Pharmacokinetic Nights 1 and 2.

- On Pharmacokinetic Night 1, subjects will receive one half of their usual and current total nightly Xyrem® dose (administered as two equally divided doses. given at bedtime, and 4 hours later).

- On Pharmacokinetic Night 2 (which will be the next night after Pharmacokinetic Night 1 or within 2 weeks of Pharmacokinetic Night 1), subjects will receive Xyrem® at their usual stable nightly dose (administered as two equally divided doses, given at bedtime, and 4 hours later).

On each of the above nights, pharmacokinetic sampling will be performed as follows:

- At the following times in relation to the first dose: 0 (pre-dose), 0.75, 1.5, 2.5, and 4 hours (pre-second dose)

- 4.75 and 8 hours after the first dose (i.e., 0.75 and 4 hours after the second dose).

6.1.3.2 Open-Label Safety Component

The open-label safety component will follow the randomized withdrawal phase of the study.

This period will allow for a total Xyrem® exposure of up to 1 year in a subset of patients (the 1-year period includes the duration of Xyrem® administration prior to and during the randomized withdrawal phase).

Patients will participate in the open-label safety period itself for the following periods depending on whether they are Xyrem®-naïve or already on Xyrem® at entry into the study, as follows:

- Patients who are already on a stable dose of Xyrem® at entry will participate in the open-label safety period for 47 weeks.

- Patients who are Xyrem®-naïve at study entry will participate in the open-label safety period for 38 to 45 weeks.

On entering the open-label safety period, all subjects will be started at a dose no higher than half the Xyrem® dose administered at the end of the stable-dose period and will then be titrated up to an optimal dose of Xyrem®, as per the judgment of the investigator. The maximum dose used will not exceed that depicted in the table in the previous section.

Patients who withdraw prematurely from the study will undergo a 2-week post-study termination visit.

Measures to assess patient compliance are to be taken consistent with the stipulations in the Written Request of March 10, 2014: data recorded in patient daily diaries and the volume of study drug solution returned at each visit are each to be evaluated.

An age-appropriate formulation of study drug is to be used.

6.1.4 Key Inclusion Criteria For All Patients

- Male or female. Age 7 to 16 years at Visit 2 for subjects on Xyrem® at study entry and at Visit 1.1 for Xyrem®-naïve subjects (to ensure that subjects are < 18 years of age). Please see the study schedule (Section 6.1.7) for further information about the aforementioned visits.

- Primary diagnosis of narcolepsy with cataplexy (Type 1 narcolepsy) meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study.

- Positive for the HLA DQB1:0602 haplotype, as determined at screening.

- Documented assent from the patient indicating that he or she is aware of the investigational nature of the study and of the required procedures and restrictions prior to participation in any protocol-related activities.

- Informed consent from parent or guardian.

- History of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Willing to spend the required number of nights (2 to 3) in a sleep laboratory for polysomnographic evaluations.

- If currently treated with Xyrem® must have been taking unchanged doses of Xyrem® (twice nightly dosing no higher than 9 g/night) and stimulants, if applicable, for the treatment of narcolepsy symptoms for at least 2 months prior to screening.

- Agreement to abstain from caffeinated-products during nights when a polysomnogram is performed.

- If currently treated with Xyrem®, must have demonstrated clinical improvement of cataplexy per investigator's clinical judgment.

- Has agreed to abstain from caffeinated products during polysomnographic and pharmacokinetic assessment nights.

- If female and of child-bearing potential, must be willing to use a method of contraception that is considered acceptable by the investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.

- If male and sexually active with a female partner must be willing to use a method of contraception that is considered acceptable by the investigator or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.

6.1.4.1 Additional Inclusion Criteria For Patients Participating In Pharmacokinetic Evaluation Component Of Study

- Must be willing to spend 2 additional nights in a sleep laboratory for polysomnographic evaluations.

- Must have been taking unchanged doses of Xyrem® (and stimulants, if applicable) for the treatment of narcolepsy symptoms for at least 2 months prior to screening.

- Documented assent from the patient indicating that he or she is aware of the investigational nature of the pharmacokinetic component of study and of the required procedures and restrictions before participation in any protocol-related activities.

- Have sufficient blood volume for pharmacokinetic sampling based on body weight in accordance with Seattle Children's Hospital guidelines or, for a particular investigational site, Institutional Review Board eligibility guidelines for pediatric blood collection pertinent to the site.

6.1.5 Key Exclusion Criteria For All Patients

- Inability of patient to understand, assent to, or follow study instructions for any reason, in the opinion of the investigator.

- Inability of parent or guardian to comply with study requirements for any reason, in the opinion of the investigator.

- Previously treated with Xyrem®, but discontinued drug on account of lack of efficacy and/or poor tolerability.

- Narcolepsy secondary to any other medical condition.
- Restless legs syndrome requiring treatment other than iron supplements.
- Succinic semi-aldehyde dehydrogenase deficiency.
- Uncontrolled hypothyroidism.
- History of seizure disorder.
- History of head trauma associated with loss of consciousness.
- Evidence of sleep-disordered breathing, including any one of the following:
    - Presence of clinically significant obstructive or central sleep apnea, as determined by the investigator or documented previously.
    - Obstructive apnea-hypopnea index > 5 for subjects 7 to 11 years of age or obstructive apnea-hypopnea index > 10 for subjects 12 to 17 years of age.
    - Oxygen saturation nadir ≤ 85% at night.
    - Clinically significant hypoventilation.
- Oxygen saturation level < 95% for at least 5 minutes on room air as measured by pulse oximetry, while fully awake during daytime monitoring. If values < 95% are observed at study sites at higher geographic elevations and are acceptable to the investigator, enrollment of the subject requires permission from the Medical Monitor.
- Past or current major thought disorder, e.g., schizophrenia, paranoia, or mania.
- Recent history of clinically significant parasomnia (e.g., sleep walking) that could significantly affect the conduct of the study.
- Current suicide risk as determined from history, Columbia-Suicide Severity Rating Scale, or previous suicide attempt.
- A T-score ≥ 65 on the Children's Depression Inventory 2nd Edition Self-Report Short Version.
- Other documented clinically significant condition (including an unstable medical condition, chronic disease other than narcolepsy with cataplexy, or history or presence of another neurological disorder) that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the investigator.

- Electrocardiogram with clinically significant deviation from normal or clinically significant physical examination findings, as per the Investigator.

- Clinically significant laboratory abnormality, as per the Investigator.

- Positive pregnancy test at screening (pregnancy tests are to be performed in any woman who reaches menarche).

- Positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, or a history of substance abuse including alcohol abuse (if the patient takes prescribed amphetamines and has a positive test for those drugs, he will not be excluded).

- Treatment with benzodiazepines, non-benzodiazepine anxiolytics, hypnotics and sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, or ethosuximide within 2 weeks prior to enrollment (discontinuation for the purposes of study enrollment is permitted if considered safe by the Investigator and approved by the Medical Monitor).

- Treatment with other drugs for cataplexy (examples provided) within 1 month of screening.

- Current treatment with oral isotretinoin.

- Inability to fast for 2 hours before the first dose through 4 hours following the last dose on nights when polysomnography or pharmacokinetic sampling is performed.

- Lack of a commitment from the parent or guardian that the home situation is safe for Xyrem® use.

- Use of any investigational agent within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.

- Allergy to local anesthetics that may be used for blood collection.

- Allergy to malic acid, sucralose/maltodextrin, or ingredients in the flavorant if used.

- Unsafe for subject to receive placebo treatment for 2 weeks, in the opinion of the investigator.

6.1.5.1 Additional Exclusion Criteria For Patients Participating In Pharmacokinetic Evaluation Component Of Study

- Hemoglobin below the lower limit of normal for age and gender at screening or at the end of the double-blind period, whichever is closer to pharmacokinetic nights.

- Use of tobacco products or products for smoking cessation within 90 days before screening, including nicotine-containing products, or history of significant use of tobacco (> 10 cigarettes or their equivalent daily) within 3 years prior to the pre-stable-dose-phase polysomnogram.

- Non-compliance with prescribed Xyrem® regimen in the 2 weeks prior to the first Pharmacokinetic Night.

6.1.6 Concomitant Medications

6.1.6.1 Prohibited Medications

- Benzodiazepines, non-benzodiazepine anxiolytics, hypnotics and sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, and ethosuximide. If a subject undergoes short-term outpatient procedures during the study and requires opioids or benzodiazepines, study drug must be held for one night while those drugs are administered; if and opioid and/or a benzodiazepine is required for multiple days, the subject must be discontinued from the study.

- Other anti-cataplectic medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors, or tricyclic antidepressants.

- Oral isotretinoin.

- Investigational drugs other than study drug.

6.1.6.2 Permitted Medications

- Stimulant therapy, as long as the dose is stable during the stable-dose and double-blind withdrawal periods.

- Vitamins in normal doses (herbal supplements are prohibited).

- Acetaminophen for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:

    - For subjects aged 7 to 11 years: no more than 325 mg every 4 to 6 hours, not to exceed 1625 mg in 24 hours.

- For subjects 12 years and older: no more than 650 mg every 4 to 6 hours, not to exceed 3250 mg in 24 hours.

- Ibuprofen for fever, headache, or other pain in accordance with the allowable dose limits by age for each country and not to exceed the limits below:

  - For subjects aged 7 to 11 years: no more than 100 mg every 6 to 8 hours, not to exceed 400 mg in 24 hours.

  - For subjects 12 years and older: no more than 200 mg every 4 to 6 hours, not to exceed 1200 mg in 24 hours.

- Birth control pills, patches, injections, or implants (all hormonal contraceptives) may be continued.

- Local topical anesthetic agent for placement of indwelling catheter or before any blood draws.

- Non-sedating antihistamines.

- Anti-inflammatories for pain.

- Chronic topical or oral antibiotics for acne.

- Over-the-counter decongestants.

6.1.7 Schedule

The study schedule is depicted in a series of tables which have been copied below from the study protocol in this supplemental NDA and are partly self-explanatory (please refer to the submission itself for further details).

Note that individual episodes of cataplexy are to be recorded in patient diaries.

6.1.7.1 Schedule For Subjects Taking Xyrem® At Study Entry (Including Open-Label Safety Component)

The study schedule for subjects taking Xyrem® at study entry is copied below from the submission.

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

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

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

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

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

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

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

b) The Screening Period for subjects with low body weight who are participating in the PK evaluation should be as close as possible to 30 days to minimize the amount of blood drawn over 30 days.

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

d) HLA DQB1:0602: Collect blood sample unless previous result available.

e) See Table 2.

f) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).

g) If PK collection is conducted in the Stable-Dose Period, collect coagulation samples during the Screening Period.

h) If PK collection is conducted during the Open-Label Period, collect coagulation samples within 30 days prior to PK Night 1.

i) Urine drug screen and alcohol test: only for subjects continuing to the Open-label Safety Period.

j) Recorded daily in electronic diary.

k) Impression of severity prior to any narcolepsy treatment.

l) C-SSRS: Use Baseline/Screening Version at Visit 1 and Since Last Visit version at all other visits for subjects ≥12 years of age, and use Children's versions for children <12 years of age.

m) School attendance collected for subjects who attend school during Stable-Dose and Double-Blind Treatment Periods.

n) Study drug quantities dispensed at study visits in accordance with protocol and as required by State or local regulation.

o) If the subject withdraws early from the study during the Open-Label Safety Period, perform a PSG if subject is willing and if the subject is willing to be dosed with study drug for this PSG night. Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.

6.1.7.2 Schedule For Subjects Who Are Xyrem®-Naïve At Study Entry (Except Open-Label Safety Component)

The study schedule for subjects who are Xyrem®-naïve at study entry is copied below from the submission.

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

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

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

		Open-Label Titration Period (up to 10 weeks) Xyrem-naïve subjects only							Stable-Dose Period		Double-Blind Treatment Period	See Appendix 2.2 for Schedule of Events for the Open-Label Safety Period
Events	Screening	Begin Titration							End Titration Begin Stable-Dose	End of Stable-Dose Begin Double-Blind Treatment	End of Double-Blind Treatment Begin Open-Label Safety	
Visits	V1	V1.1	V1.2	V1.3 Phone Call	V1.4 Phone Call	V1.5	V1.6 Phone Call	V1.7	V2	V3	V4	
Weeks (W)	Day -30 to -1[a]	Day 1	W1 +3 days	W2 +3 days	W3 +3 days	W4 ±7 days	W6 +3 days	W8 ±7 days	W10 ±3 days	W12 +3 day	W14 +3 day	
CDI2:SR[S] for depression	X	X		X		X	X	X	X	X	X	
MASC-10 for anxiety scale	X	X		X		X	X	X	X	X	X	
School Attendance Diary[i]									→	→	→	
Assess subject and determine if additional dose titration is necessary			X	X	X	X	X	X				
AE Reporting	→	→	→	→	→	→	→	→	→	→	→	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Randomize subjects										X		
Dispense Study Drug[j]		X	X			X		X	X	X	X	
Collect study drug, measure compliance			X			X		X	X	X	X	
Fasting morning blood sample: GH, IGF-1, prolactin[k]										See Appendix 2.3	X	
Breakfast										See Appendix 2.3	X	
PSG	See Appendix 2.3									See Appendix 2.3		

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

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

6.1.7.3 Schedule For Polysomnographic Procedures

6.1.7.3.1 Schedule For Patients On Xyrem® At Study Entry

Polysomnographic night procedures for patients taking Xyrem® at study are displayed in the following sponsor table.

	Screening Visit	Open-Label Safety Period with Xyrem
Visits	**V1** **Day -30 to -1**[a]	**Visit 15** **Week 52 (±7 days)** **Or Early Termination**
PSG Night Procedures[b]	Screening PSG	End of Study PSG /Early Termination
Review inclusion/exclusion criteria	X	
Light dinner >2 hours before dosing	X[c]	X[c]
Confirm Parent(s)/ Guardian(s) Contact Information	X	X
Administer or supervise the administration of Study Drug[d]	X	X
PSG	X	X[e]
$EtCO_2$ or $TcCO_2$[f]	X	X
Vital Signs[g]	X	X
Pulse Oximetry[h]	X	X
Record AEs/Concomitant Medications	X	X
Brief neurological exam[i]	X	X
Fasting morning blood sample: GH, IGF-1, prolactin		X
Breakfast (if subject prefers to eat at the study center)	X	X

a) If needed, additional screening time may be granted with permission of the Medical Monitor.
b) Perform all other procedures for the visit prior to the PSG night procedures.
c) Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or home.
d) Administer the subject's nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
e) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
f) CO_2 monitoring on PSG nights only at sites where monitoring is routinely performed.
g) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min. Obtain at pre-dose and before release from study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the 1st Xyrem dose, heart and respiratory rates recorded via PSG.
h) SpO_2 monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
i) Brief neurological exam before discharge on the morning after PSG.

6.1.7.3.2 Schedule For Patients Who Are Xyrem®-Naïve At Study Entry

Polysomnographic night procedures for patients who are Xyrem®-naïve at study are displayed in the following sponsor table.

	Screening Visit	End Stable-Dose Period Begin Double-Blind Treatment Period	Open-Label Safety Period with Xyrem
Visits	**V1 Day -30 to -1[a]**	**V3 Week 3 (± 3 days)**	**Visit 15 Week 52 (±7 days) Or Early Termination**
PSG Night Procedures[b]	Screening PSG	End of Stable-Dose/Pre-Randomization PSG	End of Study PSG /Early Termination
Review inclusion/exclusion criteria	X		
Light dinner >2 hours before dosing	X[c]	X[d]	X[d]
Confirm Parent(s)/ Guardian(s) Contact Information	X	X	X
Administer or supervise the administration of Study Drug[e]		X	X
PSG	X	X[f]	X[g]
$EtCO_2$ or $TcCO_2$[h]	X	X	X
Vital Signs[i]	X[j]	X[k]	X[k]
Pulse Oximetry	X[l]	X[m]	X[m]
Record AEs/Concomitant Medications	X	X	X
Brief neurological exam[n]	X	X	X
Fasting morning blood sample: GH, IGF-1, prolactin		X	X
Breakfast (if subject prefers to eat at the study center)	X	X	X

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

a) If needed, additional screening time may be granted with permission of the Medical Monitor.
b) Perform all other procedures for the visit prior to the PSG night procedures.
c) No food restrictions.
d) Light dinner taken >2 hours prior to dosing. The dinner should be the same or similar on all PSG nights and may be taken at the Sleep Lab or at home.
e) Administer the subject's nightly dose of Xyrem divided in two doses, at bedtime and 4 hours later while in bed.
f) End of Stable-Dose/Pre-Randomization PSG: Perform prior to Randomization.
g) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
h) CO_2 monitoring on PSG nights only at sites where monitoring is routinely performed.
i) Obtain vital signs (blood pressure, pulse/heart rate, body temperature, respiratory rate) after subject has been resting for ≥5 min.
j) Vital signs obtained prior to the start of the PSG and prior to release from study center.
k) Vital signs obtained at pre-dose and before release from the study center. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, heart and respiratory rates recorded via PSG.
l) Monitor SpO_2 to determine obstructive sleep apnea status.
m) SpO_2 monitored continuously from immediately before first dose through 8 hours post-first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. Additional measurement is taken while the subject is awake and before release from the study center.
n) Brief neurological exam before discharge on the morning after PSG.

6.1.7.4 Schedule For Open-Label Safety Component (Xyrem®-Naïve At Study Entry)

The schedule for the open-label safety component (extension) is copied below and applies specifically to patients who were Xyrem®-naïve at entry into the study (the schedule for those receiving a stable dose of Xyrem® at study entry is not substantially different).

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

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

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

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

a) Visit 5 will be conducted 4 weeks after the end of the Double-Blind Treatment Period unless Visit 5 is within 2 weeks of the Week 18 visit. Visits 6-16 will be conducted at Weeks 16, 18, 22, 26, 30, 34, 39, 43, 48, 52, and 54 after Day 1.

b) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT) collect within 30 days prior to PK Night 1.

c) Recorded daily in electronic diary.

d) Obtain vital signs after the subject has been resting for ≥5 minutes.

e) C-SSRS: Use Since Last Visit version for subjects ≥12 years of age and use Children's versions for children <12 years of age.
f) Early termination PSG does not apply for subjects who discontinue before entering the Open-Label Safety Period.
g) Study drug dispensed at study visits in accordance with protocol and as required by State or local regulation.

6.1.7.5 Schedule For Pharmacokinetic Evaluation Procedures

The schedule for pharmacokinetic evaluations (for subjects participating in that component of the study) is below.

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

a) For subjects on Xyrem at study entry participating in PK evaluations during the Stable-Dose Period, PK Night 1 will occur on the night of Day 1. For subjects participating in PK evaluations during the Open-Label Safety Period, PK Night 1 will occur after retitration to a stable dose.

b) For subjects on Xyrem at study entry participating in PK evaluations during the Stable-Dose Period, PK Night 2 will occur within 15 days of PK Night 1. For subjects participating in PK evaluations during the Open-Label Safety Period, there are no restrictions in the timing between PK Nights 1 and 2.

c) Coagulation: prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (PTT).

d) Light dinner taken >2 hours prior to dosing should be the same or similar on both PK Nights. Light meal may be taken at the clinic or at home.

e) Blood samples for sodium oxybate concentrations will be collected at 0 (pre-dose) and 0.75, 1.5, 2.5, 4 (pre-2nd dose), 4.75, and 8 hours after the first dose. Samples taken within ±5 minutes of the protocol specified time points.

f) Obtain vital signs after subject has been resting for ≥5 min. Obtain vital signs at pre-dose. At 1, 4 (pre-2nd dose), 5, and 8 hours after the first Xyrem dose, obtain pulse/heart and respiratory rates.

g) SpO_2 is monitored continuously from immediately before first dose through 8 hours after the first dose, and recorded pre-dose and at 1 h, 2 h, 4 h (pre-2nd dose), 5 h, 6 h, and 8 h after the first dose. An additional measurement will be taken while the subject is awake and before release from the study center.

h) Administer ½ of the subject's usual nightly dose in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see Section 3.1.7).

i) Administer the subject's nightly dose of Xyrem in two equally divided doses, at bedtime and 4 hours later while in bed. Subjects whose equally divided dose does not match a line on the dosing syringe will take the dose that matches the next lower printed line on the dosing syringe (see Section 3.1.7).

j) Brief neurological exam before discharge on the morning after pharmacokinetic assessment.

6.1.8 Outcome Measures

6.1.8.1 Primary Efficacy Parameter

Change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

6.1.8.1.1 Further Description Of Primary Efficacy Parameter

The weekly frequency of cataplexy attacks was derived from a diary completed by the patient with the help of a caregiver, if needed.

6.1.8.2 Key Secondary Efficacy Parameters

- Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

- Change in the modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind period.

6.1.8.2.1 Further Description Of Key Secondary Efficacy Parameters

6.1.8.2.1.1 Clinical Global Impression Of Change For Cataplexy Severity

This parameter was rated based on a 7-point Likert scale, scored as follows

Very much improved: 3.
Much improved: 2.
Minimally improved: 1.
No change: 0.
Minimally worse: -1.
Much worse: -2.
Very much worse: -3.

6.1.8.2.1.2 Epworth Sleepiness Scale For Children And Adolescents

The Epworth Sleepiness Scale for Children and Adolescents is a patient-rated measure of daytime sleepiness. Patients (assisted by their caregivers) are asked to rate their chances of dozing during each of the following 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high): sitting and reading; sitting and watching TV or a video; sitting quietly in a classroom at school during the morning; sitting or riding as a passenger in a car or bus for about half an hour; lying down to rest or nap in the afternoon; sitting and talking to someone; sitting quietly alone after lunch; and sitting and eating a meal.

6.1.8.3 Other Secondary Efficacy Parameters

- Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

- Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

6.1.8.4 Exploratory Efficacy Parameters

- Change in weekly school attendance from the end of the stable-dose period to the end of the double-blind period (if the patient does attend school during that period).

- Patient Global Impression of Change, comparing the end of the double-blind period to the end of the stable-dose period.

6.1.8.5 Safety Measures

Adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), standard safety laboratory tests (hematology, clinical chemistry, and urinalysis), assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index. Serum pregnancy tests.

Plasma carbon dioxide concentrations will also be monitored at sites where such monitoring is routinely performed, and where performance of such monitoring will not have a negative effect on study participation or on polysomnographic data integrity.

A Data Safety Monitoring Board is to review safety data for the study on a regular basis.

6.1.8.6 Pharmacokinetic Measures

Plasma concentrations of sodium oxybate.

6.1.9 Analysis Plan

6.1.9.1 General

The following populations will be used for purposes of analysis.

6.1.9.1.1 Safety Population

This population will consist of all subjects who are dispensed study drug. This population will be used for tabulations and listings of safety data and to summarize efficacy data collected during the double-blind treatment period.

6.1.9.1.2 Pharmacokinetic Half-Dose Population

This population will consist of all subjects who have any pharmacokinetic data for Pharmacokinetic Night 1 when subjects (in the pharmacokinetic analysis subset) receive only half of their usual pre-study dose. This population will be used for listings and for descriptive statistics for the half-dose pharmacokinetic data.

6.1.9.1.3 Pharmacokinetic Full-Dose Population

This population will consist of all subjects who have any pharmacokinetic data for Pharmacokinetic Night 2 when subjects (in the pharmacokinetic analysis subset) receive their usual pre-study dose. This population will be used for listings and descriptive statistics for the full-dose pharmacokinetic data.

6.1.9.1.4 Pharmacokinetic Completer Population

This population will consist of all subjects who have pharmacokinetic data for both pharmacokinetic nights. This population will be used for evaluating within-subject dose proportionality.

6.1.9.2 Efficacy Population

This 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 the primary and secondary efficacy endpoints.

6.1.9.2.1 Randomized Population

This 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 and may also be used for summarizing 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 parameters.

6.1.9.3 Demographic And Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the safety population, the pharmacokinetic half-dose population, the pharmacokinetic completer population, the randomized population, and the efficacy population. The summaries of data will include numbers and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables.

Tabulations for the randomized and efficacy populations will be by treatment group (as randomized) and for both treatment groups combined. Tables for the randomized population will include a comparison of the treatment groups with categorical variables analyzed by using a Chi-square test and continuous variables analyzed using a one-way analysis of variance model with treatment as the only factor.

6.1.9.4 Handling Of Dropouts And Missing Data

The following methods will be used to handle missing data and data from subjects who discontinue early during double-blind treatment.

- The weekly number of cataplexy attacks will be computed as the average from days with non-missing data, multiplied by 7.
- School attendance will be calculated as the number of missed days, multiplied by 100 and divided by the actual number of school days up to the timepoint of early termination or double-blind treatment period completion.
- The last post-stable-dose period assessment of all other measures will be used as the end-of-double-blind treatment period assessment.

6.1.9.5 Efficacy Parameters

The two treatment groups for the double-blind treatment period will be compared on the efficacy parameters.

Non-categorical efficacy parameters will be analyzed using a non-parametric analysis of covariance. Ordinal categorical parameters will be analyzed using Cochran-Mantel-Haenszel tests for row mean score difference.

To account for multiplicity arising as a consequence of the analysis of the primary endpoint and multiple secondary endpoints, a tiered approach will be used to control the Type 1 family-wise error rate at the two-sided significance level of 0.05 (with an exception for the analysis of the primary endpoint: see below).

Testing will not proceed to the next tier unless Xyrem® is demonstrated to have a statistically significant superiority to placebo as a result of analyses performed at the previous tier level.

The efficacy parameters will be analyzed in the same numerical order as listed below.

6.1.9.5.1 Tier 1: Primary Efficacy Parameter

The primary efficacy parameter is the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable dose period.

This parameter will be analyzed at a significance level of 0.048 (two-sided).

6.1.9.5.2 Tier 2: Key Secondary Efficacy Parameter

A key secondary efficacy parameter is the Clinical Global Impression of Change for cataplexy severity comparing the end of the double-blind period with the end of the stable dose period.

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.3 Tier 3: Key Secondary Efficacy Parameter

Another key secondary efficacy parameter is the change in the modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind period

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.4 Tier 4: Other Secondary Efficacy Parameter

A secondary efficacy parameter is the Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable dose period

This parameter will be analyzed at a significance level of 0.05 (two-sided).

6.1.9.5.5 Tier 5: Other Secondary Efficacy Parameter

A further secondary efficacy parameter is the change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

This parameter will be analyzed at a significance level of 0.05 (two-sided).

The analysis of exploratory efficacy endpoints will be conducted without adjustment for multiple comparisons: only the nominal p-value will be reported for those analyses.

6.1.9.6 Pharmacokinetic Parameters

The plasma pharmacokinetic parameters for sodium oxybate are the following: C_{max}, AUC, and T_{max} over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours and 8 hours after the first nightly dose (0.75 hours and 8 hours after the second dose, respectively) will be measured to estimate peak and residual exposure to sodium oxybate linked to the second nighttime dose.

Plasma sodium oxybate concentrations will be summarized by sampling time point and by pharmacokinetic parameter using descriptive statistics for each age group (i.e., ages 7 to 11 and 12-17) and overall.

Pharmacokinetic parameters will be assessed using analysis of covariance models and natural log-transformed data.

Dose-proportionality is to be assessed based on the ratio of AUC and C_{max} values: the ratios and 90% confidence intervals will be presented. If warranted, regression models will be used to explore the relationship between plasma concentration and dose on a mg/kg basis.

6.1.10 Safety Parameters

Safety data will be summarized using descriptive statistics.

Adverse events will be summarized by treatment group and by dose. Adverse events will be analyzed for sub-populations including the following: Xyrem®-naïve at entry; receiving Xyrem® at entry; 7-11 year age group; and 12-17 year age group.

Safety analyses will also include an evaluation of the nadir oxygen saturation level at each dose and number and duration of confirmed desaturations below 90%, 80%, 70%, 60%, and 50% on polysomnographic nights, excluding the screening polysomnogram.

6.1.10.1 Interim Analysis

An interim analysis is planned to be conducted after 35 subjects complete or discontinue early from the double-blind treatment period. The interim analysis will be conducted by a statistician not directly involved with the design and analysis of the study. The data obtained from the interim analysis will be reviewed by the study's Data Safety Monitoring Board who will recommend whether to continue the study or to halt it early.

Considerations for stopping the study early include the following:

- Treatment success: the O'Brien-Fleming approach will be used with the primary efficacy endpoint which will be tested at a significance level of 0.005 at the interim analysis; if Xyrem® is demonstrated to have a statistically significant superiority to placebo on that analysis, the Data Safety Monitoring Board may then recommend discontinuing the study; however, if the study is not stopped, the final analysis of the primary efficacy parameter will be conducted at a significance level of 0.048 so as to preserve the overall alpha of 0.05.

- Treatment failure: if at the interim analysis, the null hypothesis for the primary efficacy parameter is not rejected at the 0.005 level of significance, a futility analysis will be conducted using a conditional power approach as follows. Assuming that the trend in data observed until the time of the interim analysis will continue until the final analysis, the conditional power of rejecting the null hypothesis at final analysis will be calculated. If the conditional power is less than

15%, it will be concluded that the study is unlikely to demonstrate efficacy and the Data Safety Monitoring Board may then recommend stopping the study. The study may also be discontinued early due to futility.

- Safety concerns: safety data including the incidence of adverse events will be reviewed by the Data Safety Monitoring Board at regular intervals with deaths and serious adverse events getting special scrutiny; based on that review, the Data Safety Monitoring Board may determine if the risk to participating subjects warrants study discontinuation.

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

6.1.10.2 Sample Size Estimate

At least 100 subjects are to be enrolled in this study so that a minimum of 70 subjects enter the double-blind treatment phase.

A sample size of at least 35 subjects per treatment group entering the double-blind (randomized withdrawal) treatment period is expected to have at least 80% power to detect a difference between treatment groups of 40% in the percentage change in the mean weekly number of cataplexy attacks during the last 2 weeks of the immediately-preceding stable dose period.

6.1.11 Safety Monitoring

The following will be evaluated according to the study schedule outlined earlier: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests (hematology, clinical chemistry, and urinalysis), assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index. Plasma carbon dioxide concentrations will also be monitored at selected sites.

A Data Safety Monitoring Board is to review safety data for the study on a regular basis.

6.2 Results Of Interim Analysis And Subsequent Data Safety Monitoring Board Recommendations

As of November 27, 2015, 35 patients had completed or discontinued early from the double-blind treatment period of this study. The study protocol provided for an interim analysis of efficacy at that timepoint (as already noted above).

For the interim analysis of efficacy, study data were unblinded only for Data Safety Monitoring Board and Clinical Research Organization staff.

The Data Safety Monitoring Board met on February 24, 2016, after reviewing the results of the above interim efficacy analysis and informed the sponsor that the same analysis had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value < 0.005. Recommendations were also made by the Data Safety Monitoring Board, as outlined below.

6.2.1 Data Safety Monitoring Board Recommendations Based On Results Of Interim Analysis

The Data Safety Monitoring Board recommended the following based on the results of the interim analysis that was conducted after 35 patients had completed or discontinued the double-blind segment of the study.

- End the double-blind segment of Study 13-005, “as there are adequate data for deriving an inference of benefit in cataplexy.”
- Amend the study protocol to continue the open-label safety segment.
- Continue to enroll subjects in the open-label pharmacokinetic segment (evaluating up to 18 patients in each age-based category).

The results of the above interim analysis led to the original pediatric Written Request being amended and to the issuance of the final pediatric Written Request summarized in Section

6.3 Protocol Amendment (#4) After Interim Analysis

Based on the recommendations of the Data Safety Monitoring Board, the protocol for Study 13-005 was amended in Submission #256 (also submitted on April 18, 2016); this protocol change was designated as Amendment #4 and was dated April 5, 2016.

The main elements of the protocol amendment are below.

6.3.1 Double-Blind Segment Of Study

The double-blind (randomized withdrawal) segment of Study 13-005 is being terminated in accordance with the recommendations of the Data Safety Monitoring Board.

Subjects who have already entered or completed the double-blind segment of the study when the above protocol amendment comes into effect are to follow study procedures for those randomized to double-blind treatment.

The tiered analysis of the secondary efficacy parameters is to be conducted using a one-sided p-value of 0.05, rather than using a two-sided p-value of 0.05 as originally proposed. (Note that in the next protocol amendment, Amendment #5, the tiered analysis of the secondary efficacy parameters reverted to being conducted using a two-sided p-value of 0.05).

Under this amendment, a slight change in the dose-titration regimen for Xyrem®-naïve patients is being instituted. The new regimen is depicted in the table below.

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.

To facilitate easy comparison, the previous regimen is depicted in the table below.

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 or 1.5 g/night/week	9 g/night

*At bedtime and 2.5 to 4 hours later.
**Titration of 1 g/night/week up to 7 g/night and then 0.5 g/night/week final titration permitted.

6.3.2 Open-Label Safety Segment Of Study

The open-label phase of the study will be continued. The study will be continued until at least 100 patients have been enrolled and have had the opportunity to be titrated to an effective Xyrem dose (if Xyrem-naïve) or be treated for at least 1 month at that dose (if receiving Xyrem at study entry).

6.3.3 Open-Label Pharmacokinetic Segment Of Study

The open-label pharmacokinetic segment of the study will continue to enroll patients until the completion of the study. If is not possible to enroll more than 12 patients in each age stratum, the pharmacokinetic analysis is to be conducted using data from additional subjects enrolled at the completion of the study.

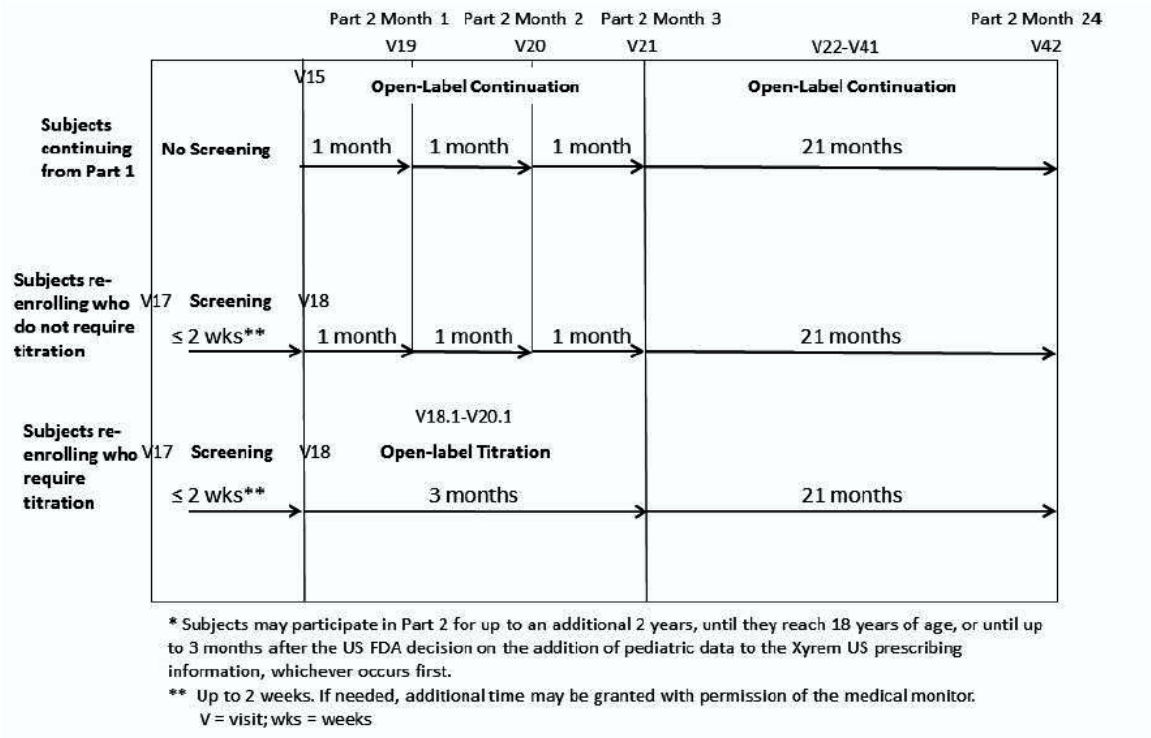
6.4 Subsequent Protocol Amendment: Amendment #5, Dated February 23, 2017 (Submitted To IND 49641 On April 6, 2017, As Serial Number 275)

Under this amendment (set of amendments), this study is divided into 2 parts

- Part 1 lasting up to one year comprises the entire protocol described in Amendment #4 and is the version of the protocol subsumed under the Written Request.

- Part 2 is a further open-label extension to Part 1. In Part 2, , a patient who completes one year of the study in Part 1 will have the opportunity to continue open-label treatment with Xyrem until the first occurrence of any one of the following: an additional 2 years of treatment; the subject reaches 18 years of age; or 3 months have passed after a future Agency decision to add pediatric information to the US Prescribing Information for Xyrem. The total duration of a subject's treatment will thus be up to 3 years. Note that a patient who has earlier completed Part 1 also has the opportunity to complete Part 2; such a patient may or may not require re-titration of Xyrem®.

The schema for Part 2 is summarized below.



Assessments during Part 2 will continue at monthly intervals and will be similar to those for Part 1.

6.5 Study Results

This study was conducted at a total of 30 sites in 5 countries. The countries in which the study was conducted were as follows: the United States (25 sites), France (2 sites), Italy (1 site), the Netherlands (1 site), and Finland (1 site).

6.5.1 Disposition

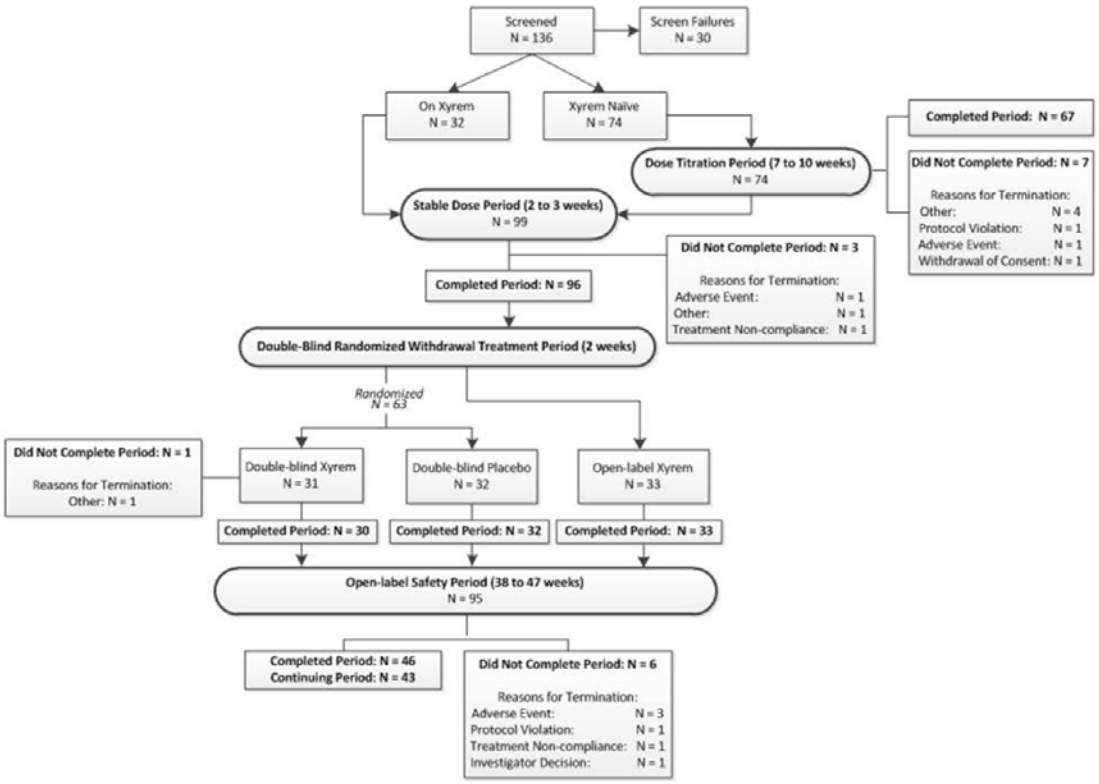
136 patients were screened for this study. 106 patients were then enrolled: of those patients, 74 were Xyrem®-naïve and 32 had previously been exposed to Xyrem®.

99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

95 patients then entered the open-label safety period (for Part 1 of the study). At the cut-off date (February 10, 2017) for the submission of the report of that study with the original sNDA submission, 46 patients had completed Part 1 of the study, whereas 43 patients were continuing in that phase. As of February 10, 2017, 17 patients had withdrawn from the study.

The disposition of study subjects is summarized in the following graphic which I have copied from the submission.



6.5.2 Protocol Deviations

A total of 42 major protocol deviations were noted in this study. I have reviewed those deviations. None appear to have been significant enough to warrant the exclusion of subjects from the efficacy population.

6.5.3 Study Populations

These are summarized in the following sponsor table.

	Age Group[a]		Xyrem Status[b]		Total
	7 to 11 years	12 to 17 years	Xyrem Naïve	On Xyrem at Entry	
Population	N = 38	N = 68	N = 74	N = 32	N = 106
Safety Population	38 (100.0)	68 (100.0)	74 (100.0)	32 (100.0)	106 (100.0)
PK Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
PK Half-dose Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
PK Full-dose Population	11 (28.9)	18 (26.5)	18 (24.3)	11 (34.4)	29 (27.4)
Efficacy Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)
Per Protocol Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)
Randomized Population	26 (68.4)	37 (54.4)	39 (52.7)	24 (75.0)	63 (59.4)

[a] Age in years at the first dispensation of study drug.
[b] Xyrem status at the time of study entry.
Note: The Safety Population consists of all subjects who were dispensed study drug. All 29 subjects completed both night 1 and night 2 of the PK assessments, and therefore the PK Half-dose population, the PK Full-dose population, and the PK Completers population were equivalent; therefore, the PK population is displayed here for simplicity. The Efficacy Population consists of subjects randomized to Xyrem or Placebo who completed at least 5 days of dosing in the Double-blind Treatment Period. The Per Protocol Population includes subjects in the Efficacy Population without a relevant major protocol deviation. The Randomized Population consists of all subjects who were randomized to either Xyrem or Xyrem Placebo for the Double-blind Treatment Period.

6.5.4 Demographic Characteristics For Several Study Populations

The next sponsor table summarizes demographic characteristics for the efficacy, safety, and pharmacokinetic populations. Age was adequately matched across the treatment groups for the efficacy populations.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Age (years)[b]				
n	32	31	106	29
Mean (SD)	11.8 (2.48)	11.6 (2.54)	11.9 (2.42)	12.0 (2.35)
Median	12.0	12.0	12.0	12.0
Min, Max	7, 16	7, 16	7, 16	8, 16
Age Group, n (%)				
7 to 11 years	14 (43.8)	12 (38.7)	38 (35.8)	11 (37.9)
12 to 17 years	18 (56.3)	19 (61.3)	68 (64.2)	18 (62.1)
Sex, n (%)				
Male	17 (53.1)	18 (58.1)	63 (59.4)	22 (75.9)
Female	15 (46.9)	13 (41.9)	43 (40.6)	7 (24.1)
Race, n (%)				
Asian	1 (3.1)	1 (3.2)	3 (2.8)	0
Black / African American	7 (21.9)	4 (12.9)	25 (23.6)	1 (3.4)
White	23 (71.9)	25 (80.6)	73 (68.9)	27 (93.1)
Other	1 (3.1)	1 (3.2)	5 (4.7)	1 (3.4)
Ethnicity, n (%)				
Hispanic / Latino	2 (6.3)	0	6 (5.7)	0
Not Hispanic / Latino	30 (93.8)	31 (100.0)	100 (94.3)	29 (100.0)
Country, n (%)				
USA	17 (53.1)	16 (51.6)	62 (58.5)	10 (34.5)
Finland	0	0	1 (0.9)	0
France	3 (9.4)	4 (12.9)	10 (9.4)	0
Italy	9 (28.1)	9 (29.0)	25 (23.6)	19 (65.5)
Netherlands	3 (9.4)	2 (6.5)	8 (7.5)	0

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population, PK = pharmacokinetic.

[a] Randomized treatment assigned during the Double-blind Treatment Period

[b] Age in years at the first dispensation of study drug.

Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period. The Safety Population consists of all subjects who were dispensed study drug. For the PK population, all 29 subjects completed both Night 1 and Night 2 of the PK assessments; therefore the PK Half-dose population, the PK Full-dose population, and the PK Completers population were equivalent. Data for the PK population is displayed here for simplicity.

6.5.5 Previous Xyrem® Experience

The previous Xyrem® experience at baseline is summarized for various study populations in the table below. The two treatment groups for the randomized, double-blind, placebo-controlled, withdrawal phase were reasonably matched in that respect.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Xyrem Status at Entry, n (%)				
Xyrem Naïve	19 (59.4)	20 (64.5)	74 (69.8)	18 (62.1)
On Xyrem at Entry	13 (40.6)	11 (35.5)	32 (30.2)	11 (37.9)
Unequal Nighttime Dosages for Subjects on Xyrem at Study Entry[b]	1 (7.7)	1 (9.1)	4 (12.5)	0
Months of Previous Xyrem Exposure				
n	14[c]	11	33	11
Mean (SD)	19.93 (14.414)	24.64 (19.185)	18.24 (15.953)	17.82 (17.566)
Median	12.50	15.00	12.00	12.00
Min, Max	7.0, 52.0	2.0, 49.0	2.0, 52.0	2.0, 48.0

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Randomized treatment assigned during the Double-blind Treatment Period.
[b] Subjects on Xyrem at study entry could maintain their typical dosing pattern during the Stable Dose Period, which could include 2 unequal dosages during the night. Percentages are calculated using the number of subjects on Xyrem.
[c] One subject (Subject (b) (6) received Xyrem prior to entering the study, and due to the amount of time between previous Xyrem exposure and start of the study, the subject was considered to be Xyrem naïve (ADSL dataset).
Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period.

6.5.6 Baseline Disease Characteristics

The sponsor table below summarizes baseline disease characteristics and is self-explanatory. The two treatment groups for the randomized, double-blind, placebo-controlled withdrawal phase were evenly matched for the following more significant characteristics: years since narcolepsy diagnosis, narcolepsy symptoms experienced previously, overall severity of narcolepsy, baseline cataplexy severity, and baseline modified Epworth Sleepiness Scale (ESS) score.

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Years from Narcolepsy Diagnosis to Screening				
n	32	31	106	29
Mean (SD)	1.94 (1.576)	1.92 (2.169)	1.86 (1.946)	1.42 (1.662)
Median	1.63	0.99	1.21	0.64
Min, Max	0.0, 4.9	0.0, 8.0	0.0, 10.4	0.0, 5.1
Narcolepsy Symptoms Experienced Prior to any Narcolepsy Treatment[b], n (%)				
Cataplexy	32 (100.0)	31 (100.0)	106 (100.0)	29 (100.0)
Excessive daytime sleepiness	32 (100.0)	31 (100.0)	106 (100.0)	29 (100.0)
Hypnagogic and / or Hypnopompic Hallucinations	16 (50.0)	16 (51.6)	60 (56.6)	12 (41.4)
Sleep Paralysis	8 (25.0)	8 (25.8)	37 (34.9)	9 (31.0)
Disrupted Nighttime Sleep	25 (78.1)	27 (87.1)	89 (84.0)	28 (96.6)
Current Narcolepsy Symptoms[b], n (%)				
Cataplexy	30 (93.8)	30 (96.8)	103 (97.2)	29 (100.0)
Excessive daytime sleepiness	31 (96.9)	27 (87.1)	99 (93.4)	26 (89.7)
Hypnagogic and / or Hypnopompic Hallucinations	12 (37.5)	11 (35.5)	44 (41.5)	5 (17.2)
Sleep Paralysis	5 (15.6)	5 (16.1)	28 (26.4)	6 (20.7)
Disrupted Nighttime Sleep	22 (68.8)	20 (64.5)	76 (71.7)	23 (79.3)
Typical Bedtime, n (%)				
20:00 to 21:59	19 (59.4)	20 (64.5)	60 (56.6)	10 (34.5)
22:00 to 23:59	13 (40.6)	11 (35.5)	43 (40.6)	19 (65.5)
00:00 to 02:00	0	0	3 (2.8)	0
Typical Hours of Sleep per Night				
n	32	31	106	29
Mean (SD)	09:16 (00:55)	09:14 (00:57)	09:11 (00:58)	08:50 (00:33)
Median	09:00	09:15	09:00	09:00
Min, Max	07:30, 11:15	07:30, 11:30	06:00, 12:00	07:50, 10:00
CGIs for Historical Condition Prior to any Narcolepsy Treatment				
Narcolepsy Overall Severity, n (%)				
0 = Normal; no signs of illness	0	0	0	0
1 = Borderline ill	0	0	1 (0.9)	0
2 = Slightly ill	0	1 (3.2)	2 (1.9)	0
3 = Moderately ill	5 (15.6)	5 (16.1)	17 (16.0)	1 (3.4)
4 = Markedly ill	19 (59.4)	17 (54.8)	56 (52.8)	22 (75.9)
5 = Severely ill	8 (25.0)	7 (22.6)	25 (23.6)	6 (20.7)
6 = Among the most Extremely ill	0	1 (3.2)	5 (4.7)	0
Mean (SD)	4.1 (0.64)	4.1 (0.81)	4.1 (0.86)	4.2 (0.47)

	Efficacy Population		Safety Population	PK Population
	Placebo[a] N = 32	Xyrem[a] N = 31	N = 106	N = 29
Cataplexy Severity, n (%)				
0 = Normal; no signs of illness	0	0	0	0
1 = Borderline ill	1 (3.1)	0	1 (0.9)	1 (3.4)
2 = Slightly ill	1 (3.1)	1 (3.2)	4 (3.8)	0
3 = Moderately ill	5 (15.6)	5 (16.1)	25 (23.6)	3 (10.3)
4 = Markedly ill	17 (53.1)	15 (48.4)	49 (46.2)	21 (72.4)
5 = Severely ill	7 (21.9)	7 (22.6)	22 (20.8)	4 (13.8)
6 = Among the most Extremely ill	1 (3.1)	3 (9.7)	5 (4.7)	0
Mean (SD)	4.0 (0.97)	4.2 (0.95)	4.0 (0.94)	3.9 (0.75)
Baseline ESS (CHAD)[c]				
n	32	31	106	29
Mean (SD)	13.9 (3.86)	13.2 (4.69)	14.3 (4.18)	13.8 (4.10)
Median	14.0	13.0	14.0	13.0
Min, Max	6, 22	5, 22	5, 22	6, 22
0 to 10 (Normal), n (%)	7 (21.9)	9 (29.0)	21 (19.8)	5 (17.2)
11 to 12 (Mildly Increased), n (%)	3 (9.4)	6 (19.4)	14 (13.2)	8 (27.6)
13 to 15 (Moderately Increased), n (%)	11 (34.4)	7 (22.6)	28 (26.4)	7 (24.1)
≥ 16 (Greatly Increased), n (%)	11 (34.4)	9 (29.0)	43 (40.6)	9 (31.0)
Baseline SF-10 Physical Summary Score				
n	30	30	99	28
Mean (SD)	41.56 (13.802)	43.04 (14.045)	42.61 (13.359)	45.16 (13.069)
Median	46.19	48.47	47.00	48.47
Min, Max	-0.9, 57.2	10.4, 57.2	-0.9, 57.2	-0.9, 57.2
Baseline SF-10 Psychosocial Summary Score				
n	30	30	99	28
Mean (SD)	49.48 (8.043)	50.96 (8.933)	50.35 (8.110)	53.27 (6.393)
Median	51.59	52.93	51.59	54.26
Min, Max	35.5, 59.6	32.9, 62.3	32.9, 62.3	34.7, 62.3

Abbreviations: CHAD = children and adolescents; ESS = Epworth Sleepiness Scale; Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Randomized treatment assigned during the Double-blind Treatment Period.
[b] Subjects may have experienced more than one of the narcolepsy symptoms. Subjects are counted in each row according to the symptoms experienced.
[c] Note that some subjects were on Xyrem at baseline and the majority were taking stimulants.
Note: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who completed at least 5 days of dosing in the Double Blind Treatment Period.

6.5.7 Exposure To Xyrem®

The total exposure to Xyrem® over all treatment periods in the safety population during this study is summarized in the next sponsor table.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 38	12 to 17 N = 68	Xyrem Naïve N = 74	On Xyrem N = 32	N = 106
Duration of Xyrem Usage (days)[b]					
n	37	67	72	32	104
Mean (SD)	288.2 (108.09)	256.2 (114.83)	256.7 (122.01)	292.2 (86.21)	267.6 (113.00)
Median	350.0	306.0	331.5	339.0	332.0
Q1, Q3	253.0, 355.0	138.0, 358.0	141.5, 357.0	246.0, 356.0	170.5, 357.0
Cumulative Xyrem Dosage Received (g)[c]					
n	37	67	72	32	104
Mean (SD)	1464.699 (705.8272)	1502.194 (834.3530)	1461.639 (846.4565)	1550.089 (644.3295)	1488.854 (787.7335)
Median	1543.000	1626.000	1592.625	1736.000	1607.250
Q1, Q3	1056.500, 1937.750	801.500, 2246.000	803.000, 2220.625	1154.250, 2019.300	859.250, 2112.875

Abbreviations: Q1 = first quartile; Q3 = third quartile.
[a] Age in years at the first dispensation of study drug.
[b] For subjects who received Xyrem during the Double-blind Treatment Period, this duration was the same as the Total Duration of Dosing. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equaled the Total Duration of Dosing minus Duration of Treatment during the Double-blind Treatment Period.

The extent of study drug exposure during the stable dose period in the safety population (who had study drug dispensed during that period) is in the next sponsor table. Note that the lowest individual total nightly dose of Xyrem® dispensed during that period was 3 grams.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 36	12 to 17 N = 63	Xyrem Naïve N = 67	On Xyrem N = 32	N = 99
Stable Dose Period Dosage Dispensed (g/night)					
n	36	63	67	32	99
Mean (SD)	6.007 (1.7139)	6.996 (1.4732)	6.922 (1.7458)	6.039 (1.1607)	6.636 (1.6281)
Median	6.000	7.000	7.500	6.000	7.000
Q1, Q3	4.500, 7.250	6.000, 8.000	5.500, 8.500	5.000, 7.000	5.500, 8.000
Min, Max	3.00, 9.00	3.75, 9.00	3.00, 9.00	3.50, 7.50	3.00, 9.00
Stable Dose Period Dosage Dispensed (mg/kg/night)[b]					
n	36	63	67	32	99
Mean (SD)	141.447 (53.3810)	105.669 (30.5447)	117.640 (36.3483)	120.855 (56.6481)	118.679 (43.6711)
Median	127.275	102.612	111.421	110.346	111.317
Q1, Q3	104.818, 176.619	83.519, 127.592	91.019, 142.857	78.265, 139.876	87.940, 142.276
Min, Max	64.81, 304.88	46.51, 182.19	46.58, 239.73	46.51, 304.88	46.51, 304.88

Abbreviations: Q1 = first quartile; Q3 = third quartile.
[a] Age in years at the first dispensation of study drug.
[b] Calculated as Xyrem dosage (g/night) * 1000 / weight (kg), where the weight is the value collected closest to but prior to or on the date of Visit 2 (Start of the Stable Dose Period).
Note: The Safety Population consists of all subjects who were dispensed study drug.

The extent of exposure to individual nightly doses of Xyrem® and its placebo equivalent in those randomized during the double-blind treatment period (and in those who received open-label Xyrem® concurrently) is in the next sponsor table, which is self-explanatory; note that the minimum dose of Xyrem® taken during that period was 3.0 grams/night.

	Treatment Received				
	Randomized Placebo [1] (N=32)	Randomized Xyrem [1] (N=31)	OL Xyrem (N=33)	All Xyrem (N=64)	Total (N=96)
Double-Blind Treatment Period Dose Level Dispensed (g/night)					
n	32	31	33	64	96
Mean (Std. Dev.)	6.672 (1.5534)	6.492 (1.6412)	6.576 (1.7650)	6.535 (1.6932)	6.581 (1.6410)
Median	6.750	7.000	7.000	7.000	7.000
Q1, Q3	5.750, 7.500	5.000, 7.500	5.500, 8.000	5.250, 8.000	5.500, 7.500
Min - Max	3.50 - 9.00	3.00 - 9.00	3.00 - 9.00	3.00 - 9.00	3.00 - 9.00
3 g/night, n (%)	0	1 (3.2)	1 (3.0)	2 (3.1)	2 (2.1)
3.5 g/night, n (%)	2 (6.3)	0	0	0	2 (2.1)
3.75 g/night, n (%)	0	1 (3.2)	1 (3.0)	2 (3.1)	2 (2.1)
4 g/night, n (%)	0	1 (3.2)	3 (9.1)	4 (6.3)	4 (4.2)
4.5 g/night, n (%)	2 (6.3)	2 (6.5)	2 (6.1)	4 (6.3)	6 (6.3)
5 g/night, n (%)	2 (6.3)	3 (9.7)	1 (3.0)	4 (6.3)	6 (6.3)
5.5 g/night, n (%)	2 (6.3)	3 (9.7)	1 (3.0)	4 (6.3)	6 (6.3)
6 g/night, n (%)	4 (12.5)	2 (6.5)	6 (18.2)	8 (12.5)	12 (12.5)
6.25 g/night, n (%)	0	0	1 (3.0)	1 (1.6)	1 (1.0)
6.5 g/night, n (%)	4 (12.5)	2 (6.5)	0	2 (3.1)	6 (6.3)
7 g/night, n (%)	4 (12.5)	5 (16.1)	3 (9.1)	8 (12.5)	12 (12.5)
7.5 g/night, n (%)	6 (18.8)	4 (12.9)	4 (12.1)	8 (12.5)	14 (14.6)
8 g/night, n (%)	0	2 (6.5)	3 (9.1)	5 (7.8)	5 (5.2)
8.5 g/night, n (%)	1 (3.1)	2 (6.5)	3 (9.1)	5 (7.8)	6 (6.3)
9 g/night, n (%)	5 (15.6)	3 (9.7)	4 (12.1)	7 (10.9)	12 (12.5)

Note: The Safety Population consists of all subjects who were dispensed study drug.
N= the total number of subjects in the population. Percentages are calculated using the N value.
[1] Subjects receive randomized treatment of Placebo or Xyrem.
[2] Calculated as Xyrem dosage [g/night] * 1000 / weight (kg), where the weight is the value collected closest to but prior to or on the date of Visit 2 (Start of the Stable-Dose Period).

6.5.8 Extent Of Stimulant Use

The extent of stimulant use during the stable dose phase and the open-label treatment period is in the next sponsor table, which I have copied from the submission.

	Stable Dose Period N = 99	Double-blind Treatment Period N = 96
Number of subjects prescribed stimulants, n (%)	55 (56.1)	53 (55.8)
Number of subjects who took all doses of prescribed stimulants, n (%)	39 (70.9)	40 (75.5)
Number of subjects who took a portion of prescribed stimulants, n (%)	14 (25.5)	12 (22.6)
Centrally Acting Sympathomimetics	49 (49.5)	47 (49.0)
Methylphenidate / methylphenidate hydrochloride [a]	18 (18.2)	18 (18.8)
Modafinil	17 (17.2)	16 (16.7)
Armodafinil	7 (7.1)	7 (7.3)
Obetrol / Amfetamine Sulfate [b]	11 (11.1)	10 (10.4)
Lisdexamfetamine mesilate	1 (1.0)	1 (1.0)

[a] One subject (Subject (b) (6) was prescribed Methylphenidate and Methylphenidate hydrochloride (Listing 16.2.4.4).
[b] One subject (Subject (b) (6) was prescribed Obetrol and Amfetamine Sulfate (Listing 16.2.4.4).

Importantly, during the double-blind treatment period, stimulant use occurred in 18/32 (56.3%) of patients who received placebo and 17/31 (54.8%) of patients who received Xyrem®.

6.5.9 Treatment Compliance

Treatment compliance by study period for the safety population is in the next sponsor table. Treatment compliance was matched in the 2 treatment groups during the double-blind withdrawal phase.

	Dose Titration Period	Stable Dose Period	Double-blind Treatment Period			Open-label Safety Period
	Total N = 74	Total N = 99	Randomized Placebo N = 32	Randomized Xyrem N = 31	Open-label Xyrem N = 33	Total N = 95
Percent Compliance[a]						
n	71	98	32	31	32	94
Mean (SD)	83.99 (16.448)	87.77 (15.775)	93.73 (7.836)	92.81 (10.653)	80.82 (17.553)	81.78 (17.202)
Median	89.20	93.30	96.40	100.00	82.70	88.20
Q1, Q3	79.60, 95.00	85.30, 96.70	86.95, 100.00	92.30, 100.00	74.15, 96.90	76.30, 93.10
< 75%, n (%)	14 (18.9)	11 (11.1)	1 (3.1)	3 (9.7)	8 (24.2)	21 (22.1)
≥ 75% to ≤ 90%, n (%)	24 (32.4)	27 (27.3)	9 (28.1)	4 (12.9)	15 (45.5)	34 (35.8)
> 90%, n (%)	33 (44.6)	60 (60.6)	22 (68.8)	24 (77.4)	9 (27.3)	39 (41.1)
Missing, n (%)	3 (4.1)	1 (1.0)	0	0	1 (3.0)	1 (1.1)
Bottle Weight Percent Compliance[b]						
n	68	96	32	31	33	50
Mean (SD)	88.49 (18.100)	100.19 (13.322)	105.46 (5.948)	101.74 (10.324)	98.33 (17.464)	101.51 (12.681)
Median	94.00	101.60	104.70	102.70	101.00	101.85
Q1, Q3	74.70, 102.55	97.05, 104.55	102.60, 109.35	101.20, 107.00	95.20, 104.60	97.60, 104.40
< 75%, n (%)	17 (23.0)	4 (4.0)	0	1 (3.2)	2 (6.1)	1 (1.1)
≥ 75% to ≤ 90%, n (%)	13 (17.6)	5 (5.1)	0	1 (3.2)	4 (12.1)	3 (3.2)
> 90%, n (%)	38 (51.4)	87 (87.9)	32 (100.0)	29 (93.5)	27 (81.8)	46 (48.4)
Missing, n (%)	6 (8.1)	3 (3.0)	0	0	0	45 (47.4)

Abbreviations: Q1 = first quartile; Q3 = third quartile.

[a] Percent compliance was determined using the daily morning diaries. Subjects were expected to take 2 doses of medication per night. Percent compliance was calculated as the number of doses taken during the period and divided by 2 times the number of days in the period, starting from the first dispense to the last date in the treatment period.

[b] Bottle Weight compliance is calculated as the amount taken during the period (measured in mL) based on the amount actually taken, determined by the total amount dispensed and the total amount returned in the bottles dispensed during the period and divided by the expected amount to be taken. Note the required estimation performed to measure amount of study drug returned in the bottles. See Section 9.4.8.

6.5.10 Efficacy Results

All efficacy analyses were conducted according to the study protocol. The results that are summarized below are those of the final efficacy analyses (and do not include those of the interim efficacy analysis, already briefly mentioned above in Section 6.2 and further described below in Section 10.1)

6.5.10.1 Primary Efficacy Analysis

The primary efficacy analysis (or Tier 1 of the hierarchical series of efficacy analyses that were conducted) compared the Xyrem® and placebo groups on the change in weekly frequency of all cataplexy attacks from baseline (the last 2 weeks of the stable dose period) over the randomized, double-blind, placebo-controlled, withdrawal period.

The results of the primary efficacy analysis are in the next sponsor table. As the table indicates, a statistically significant superiority of Xyrem® over placebo was seen on this measure, with a greater increase in cataplexy frequency in those administered placebo than in those continuing Xyrem® during the randomized, double-blind, placebo-controlled withdrawal period.

Weekly Number of Cataplexy Attacks	Placebo N = 32	Xyrem N = 31
Baseline [a] (Last 2 weeks of Stable Dose Period)		
n	32	31
Mean (SD)	16.59 (33.162)	9.60 (13.839)
Median	4.67	3.50
Q1, Q3	1.00, 11.00	0.58, 10.77
Double-blind Treatment Period		
Weekly Number of Cataplexy Attacks[b]		
n	32	31
Mean (SD)	33.96 (46.290)	12.11 (17.361)
Median	21.25	3.77
Q1, Q3	6.93, 26.35	1.50, 17.73
Change from Baseline		
n	32	31
Mean (SD)	17.37 (23.887)	2.52 (7.115)
Median	12.71	0.27
Q1, Q3	3.44, 19.77	-1.00, 2.50
p-value[c]	< 0.0001	

Abbreviations: N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.
[a] Baseline number is calculated from the last 14 days of the Stable Dose Period.
[b] Weekly number is calculated from all days within the Double-blind Treatment Period.
[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and baseline count as a covariate.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. This is the Tier 1 endpoint. Further statistical testing of Tier 2 to Tier 5 endpoints was conditional on meeting statistical significance for the Tier 1 endpoint; see

Subgroup analyses showed that the above effect was also seen within the two age-group categories: 7 to 11 years, and 12 to 17 years. The results of the subgroup analyses are in the next sponsor table.

Weekly Number of Cataplexy Attacks	7 to 11 years N = 26		12 to 17 years N = 37	
	Placebo N = 14	Xyrem N = 12	Placebo N = 18	Xyrem N = 19
Baseline [a] (Last 2 weeks of Stable Dose Period)				
n	14	12	18	19
Mean (SD)	19.14 (34.292)	12.39 (17.968)	14.61 (33.116)	7.83 (10.649)
Median	5.63	3.00	2.80	4.00
Q1, Q3	2.15, 12.92	0.50, 19.36	0.00, 7.50	1.62, 10.00
Double-blind Treatment Period				
Entire Period[b]				
n	14	12	18	19
Mean (SD)	42.58 (49.313)	16.02 (24.138)	27.25 (44.032)	9.64 (11.386)
Median	22.27	3.25	15.50	6.53
Q1, Q3	14.58, 61.00	1.33, 26.75	5.25, 22.50	1.62, 10.00
Change from Baseline				
n	14	12	18	19
Mean (SD)	23.45 (20.765)	3.63 (10.311)	12.64 (25.626)	1.81 (4.249)
Median	18.32	0.13	9.39	0.58
Q1, Q3	7.58, 35.75	-1.15, 2.05	1.08, 16.12	-0.88, 2.58
p-value[c]	0.0001		0.0044	

Abbreviations: N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.
[a] Baseline number is calculated from the last 14 days of the Stable Dose Period.
[b] Weekly number is calculated from all days within the Double-blind Treatment Period. Missing values in the Double-blind Treatment Period are imputed using the value from the Stable Dose Period (baseline observation carried forward).
[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline count as a covariate. The p-values for the subgroup analyses are considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period.

6.5.10.2 Analysis Of Key Secondary Efficacy Endpoints

6.5.10.2.1 Clinical Global Impression Of Change For Cataplexy Severity

Tier 2 of the hierarchical sequence of efficacy analyses stipulated in the study protocol analyzed scores on the Clinical Global Impression of Change for cataplexy severity. This analysis compared the end of the randomized, double-blind, placebo-controlled withdrawal period with the end of the stable dose period.

The results of the analysis of that measure are summarized in the following table provided by the sponsor. Xyrem® displayed a statistically significant superiority to placebo on that measure: cataplexy became more severe in patients receiving placebo than in those continuing Xyrem® during that period.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	32		29
Very Much Worse (-3)	4 (12.5)		1 (3.4)
Much Worse (-2)	17 (53.1)		4 (13.8)
Minimally Worse (-1)	7 (21.9)		6 (20.7)
No Change (0)	2 (6.3)		15 (51.7)
Minimally Improved (1)	0		1 (3.4)
Much Improved (2)	2 (6.3)		2 (6.9)
Very Much Improved (3)	0		0
Missing	0		2
Mean (SD)	-1.5 (1.19)		-0.4 (1.12)
p-value[b]		0.0006	
Much Worse or Very Much Worse	21 (65.6)		5 (17.2)
p-value[c]		0.0001	

Abbreviations: CGIc = Clinical Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The CGIc for cataplexy severity is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.10.2.2 Change In Epworth Sleepiness Scale (For Children And Adolescents) Score

Tier 3 of the hierarchical sequence of efficacy analyses stipulated in the study protocol compared the change in modified Epworth Sleepiness Scale score from the end of the stable-dose period to the end of the double-blind randomized withdrawal period between the Xyrem® and placebo groups. The results of that analysis are in the next sponsor table. A statistically significant superiority of Xyrem® over placebo was seen on this parameter for which scores increased in those receiving placebo to a greater extent than in those who continued to receive Xyrem®.

	Placebo N = 32	Xyrem N = 31
Baseline Value[a] (Visit 3 - End of Stable Dose Period)		
n	31	30
Mean (SD)	10.4 (3.80)	8.5 (4.35)
Median	11.0	8.0
Q1, Q3	7.0, 13.0	6.0, 11.0
0 to 10 (Normal), n (%)	15 (48.4)	22 (73.3)
11 to 12 (Mildly Increased), n (%)	6 (19.4)	4 (13.3)
13 to 15 (Moderately Increased), n (%)	8 (25.8)	1 (3.3)
≥ 16 (Greatly Increased), n (%)	2 (6.5)	3 (10.0)
Visit 4 (End of Double-blind Treatment Period)[b]		
Observed Value		
n	31	30
Mean (SD)	13.2 (4.03)	9.2 (4.81)
Median	12.0	9.0
Q1, Q3	11.0, 16.0	6.0, 11.0
0 to 10 (Normal), n (%)	7 (22.6)	21 (70.0)
11 to 12 (Mildly Increased), n (%)	9 (29.0)	3 (10.0)
13 to 15 (Moderately Increased), n (%)	5 (16.1)	3 (10.0)
≥ 16 (Greatly Increased), n (%)	10 (32.3)	3 (10.0)
Change from Baseline		
n	31	30
Mean (SD)	2.8 (3.68)	0.7 (3.22)
Median	3.0	0.0
Q1, Q3	1.0, 5.0	-1.0, 2.0
p-value[c]	0.0004	

Abbreviations: ESS (CHAD) = Epworth Sleepiness Scale for Children and Adolescents; N= the total number of subjects in the population; Q1 = first quartile; Q3 = third quartile.

[a] Baseline value is the value collected at Visit 3 (End of Stable Dose/Start of Double-blind treatment period).

[b] Missing values at the end of the Double-blind Treatment Period are imputed using the value from the Stable Dose Period (baseline observation carried forward).

[c] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate.

Notes: ESS (CHAD) Total score ranges from 0 to 24. The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. Percentages are calculated using the total number of observed values.

6.5.10.3 Analysis Of Other Secondary Endpoints And Exploratory Endpoints.

6.5.10.3.1 Clinical Global Impression Of Change For Narcolepsy Overall

Tier 4 of the hierarchical sequence of efficacy analyses stipulated in the study protocol analyzed scores on the Clinical Global Impression of Change for overall narcolepsy severity. These scores compared the end of the randomized, double-blind, placebo-controlled withdrawal period with the end of the stable dose period.

The results of the analysis of that measure are summarized in the following table provided by the sponsor. Xyrem® displayed a statistically significant superiority to placebo on that measure: narcolepsy (overall) became more severe in patients receiving placebo than in those continuing Xyrem® during that period.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	32		29
Very Much Worse (-3)	2 (6.3)		0
Much Worse (-2)	17 (53.1)		3 (10.3)
Minimally Worse (-1)	9 (28.1)		10 (34.5)
No Change (0)	2 (6.3)		14 (48.3)
Minimally Improved (1)	0		0
Much Improved (2)	2 (6.3)		2 (6.9)
Very Much Improved (3)	0		0
Missing	0		2
Mean (SD)	-1.4 (1.13)		-0.4 (0.95)
p-value[b]		0.0008	
Worsened, n (%)			
Much Worse or Very Much Worse	19 (59.4)		3 (10.3)
p-value[c]		< 0.0001	

Abbreviations: CGIc = Clinical Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory.
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The CGIc for narcolepsy overall is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.10.3.2 Other Endpoints

The Xyrem® and placebo groups for the randomized, double-blind, placebo-controlled withdrawal period were compared on a number of other secondary and exploratory outcome measures: quality of life based on Short Form-10 (physical summary score and psychosocial summary score (Tier 5); weekly school attendance (number of days missed); and Patient Global Impression of Change for narcolepsy severity overall. The differences between treatment groups were not even nominally statistically significant for the measures of quality of life and school attendance.

On the Patient Global Impression of Change for narcolepsy severity overall (which was scored and analyzed in a manner similar to the Clinician Global Impression of Change for cataplexy severity and narcolepsy severity overall), a nominally statistically significant difference between treatment groups was seen as indicated in the table below. This analysis was not part of the hierarchical sequence of analyses specified in the statistical analysis plan.

	Placebo N = 32		Xyrem N = 31
Response, n (%)			
Total Observed[a]	29		30
Very Much Worse (-3)	2 (6.9)		0
Much Worse (-2)	12 (41.4)		5 (16.7)
Minimally Worse (-1)	11 (37.9)		4 (13.3)
No Change (0)	2 (6.9)		13 (43.3)
Minimally Better (1)	2 (6.9)		4 (13.3)
Much Better (2)	0		3 (10.0)
Very Much Better (3)	0		1 (3.3)
Missing	3		1
Mean (SD)	-1.3 (0.97)		0.0 (1.30)
p-value[b]		0.0001	
Worsened, n (%)			
Much Worse or Very Much Worse	14 (48.3)		5 (16.7)
p-value[c]		0.0094	

Abbreviations: PGIc = Patient Global Impression of Change
[a] Percentages were calculated using the total number of observed values.
[b] P-value from Cochran-Mantel-Haenszel (CMH) test for Row Mean Scores Difference.
[c] P-value from Pearson's chi-square test. P-value is considered exploratory
Notes: The Efficacy Population consists of subjects randomized to Xyrem or Placebo and who complete at least 5 days of dosing in the Double-blind Treatment Period. The PGIc for narcolepsy overall is evaluated at the end of the Double-blind Treatment Period. Scores associated with the responses are mapped to 3 for very much improved, to -3 for very much worse.

6.5.11 Safety Results

6.5.11.1 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

There were no deaths during this study.

Serious adverse events that occurred during this study are summarized in the next sponsor table.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Severe
13 / Male / White		*Acute Psychosis*		Recovered / Resolved
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Moderate
14 / Male / White		*Suicidal ideation*		Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

Discontinuations due to adverse events are in the next table taken from the submission.

Subject Number Age[a] / Sex / Race	Treatment Period of Onset	System Organ Class *Preferred Term*	Relationship to Study Drug *Severity; Outcome*
(b) (6) 15 / Male / White	Dose Titration Period	Psychiatric disorders *Hallucination, tactile*	Related *Moderate; Recovered / Resolved*
(b) (6) 14 / Male / White	Dose Titration Period	Psychiatric disorders *Suicidal ideation*	Related *Moderate; Recovered / Resolved*
(b) (6) 13 / Female / White	Stable Dose Period	Investigations *Weight decreased*	Related *Mild; Recovered / Resolved*
(b) (6) 8 / Male / White	Double-blind Treatment Period; *(Open-label Xyrem)*	Respiratory Thoracic and Mediastinal Disorders *Sleep apnoea syndrome*	Related *Moderate; Recovered / Resolved*
(b) (6) 14 / Male / Black	Open-label Safety Period	Psychiatric disorders *Affect lability*	Related *Mild; Recovered / Resolved*

I have reviewed the above cases of serious adverse events and/or discontinuations due to adverse events further.

Brief narratives, based on data provided by the sponsor in this submission, are provided below for three of the above patients who had serious adverse events and/or discontinued treatment because of adverse events. They have been selected for further description because of the nature of the adverse events seen. The other adverse events in the above tables do not warrant further description.

Patient (b) (6) (adverse event: acute psychosis) was a 13-year-old boy who had been diagnosed to have narcolepsy over 2 years prior to being enrolled in Study 13-005 and weighed 64 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were marked at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate in a dose of 75 mg QD. His Xyrem® dose was titrated upwards to 8 g/night over approximately 1 month. After approximately 2 days at that dose, he developed agitation, delusions, and hallucinations (and was diagnosed to have an acute psychosis). A further 2 weeks later, Xyrem® was discontinued, but begun again yet another 2 weeks later at a dose of 4.5 g/night. His symptoms then resolved while continuing to take Xyrem® in that dose for a further 5 months.

Patient (b) (6) (adverse event: suicidal ideation) was a 14-year-old boy who had been diagnosed to have narcolepsy about 1.5 years prior to being enrolled in Study 13-005 and weighed 76 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were marked at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate in a dose of 10 mg BID. He had no prior personal or family history of depression. 2 days after beginning Xyrem® at a dose of 4.5 g/night, he developed suicidal thoughts which then increased in severity resulting in study medication being discontinued about 12 days after it was first begun. His suicidal thoughts resolved a further 2 days later.

Patien (b) (6) (adverse event: sleep apnea) was an 8-year-old boy who had been diagnosed to have narcolepsy slightly less than 2 years prior to being enrolled in Study 13-005 and weighed 46.9 kg. He had cataplexy, excessive daytime sleepiness, and other symptoms of narcolepsy, all of which were moderate at study entry. He was Xyrem®-naïve at study entry but was taking methylphenidate (controlled-release) in a dose of 27 mg QD. His Xyrem® dose was begun at 4.5 g/night and was titrated upwards to 6 g/night (3 g twice nightly); after taking the latter dose for about 2 weeks. Polysomnography showed episodes of central sleep apnea that occurred mainly after the second nightly dose of Xyrem® with brief periods of oxygen desaturation with a pO2 as low as 83%. Despite a reduction in Xyrem® dose to 4.5 g/night (2.25 g twice nightly) and later to 4 g/night (2 g twice nightly), periods of sleep apnea and oxygen desaturation continued to occur on polysomnography. Xyrem® was then permanently discontinued and follow-up polysomnography revealed no evidence of sleep apnea.

6.5.11.2 All Adverse Events

An overall summary of adverse events across all treatment periods is in the sponsor table below and is self-explanatory.

	Age (years)[a]		Xyrem Status at Entry[b]		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs	**28 (75.7)**	**47 (70.1)**	**55 (76.4)**	**20 (62.5)**	**75 (72.1)**
Any Related TEAEs[c]	18 (48.6)	34 (50.7)	43 (59.7)	9 (28.1)	52 (50.0)
Any TEAEs Leading to Drug Interruption	3 (8.1)	2 (3.0)	5 (6.9)	0	5 (4.8)
Any TEAEs Leading to Drug Withdrawal	1 (2.7)	4 (6.0)	5 (6.9)	0	5 (4.8)
Any Severe TEAEs	0	4 (6.0)	4 (5.6)	0	4 (3.8)
Any Serious TEAEs	0	2 (3.0)	2 (2.8)	0	2 (1.9)
Any Fatal TEAEs	0	0	0	0	0
Any TEAEs of Special Interest	13 (35.1)	21 (31.3)	25 (34.7)	9 (28.1)	34 (32.7)

Abbreviations: TEAE = treatment emergent adverse event.
[a] Age in years at the first dispensation of study drug.
[b] Xyrem status at the time of study entry.
[c] Related TEAEs included events considered by the Investigator to be related or suspected to be related to study drug.
Note: Percentages are calculated using the N value. This table includes events with onset during any period of the study. Events with onset more than 30 days after the last dose of study drug in the study are excluded.

The overall incidence of adverse events reported in ≥ 5% of subjects in each age group and prior Xyrem®-status category across all treatment periods by system organ class and Preferred Term is in the next sponsor table.

System Organ Class Preferred Term	Age[a] (years)		Xyrem Status at Study Entry		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs, n (%)	**28 (75.7)**	**46 (68.7)**	**55 (76.4)**	**19 (59.4)**	**74 (71.2)**
Gastrointestinal disorders	**14 (37.8)**	**22 (32.8)**	**31 (43.1)**	**5 (15.6)**	**36 (34.6)**
Nausea	6 (16.2)	12 (17.9)	16 (22.2)	2 (6.3)	18 (17.3)
Vomiting	9 (24.3)	8 (11.9)	15 (20.8)	2 (6.3)	17 (16.3)
Abdominal pain	2 (5.4)	1 (1.5)	3 (4.2)	0	3 (2.9)
Infections and infestations	**9 (24.3)**	**16 (23.9)**	**19 (26.4)**	**6 (18.8)**	**25 (24.0)**
Nasopharyngitis	3 (8.1)	4 (6.0)	7 (9.7)	0	7 (6.7)
Upper respiratory tract infection	2 (5.4)	3 (4.5)	4 (5.6)	1 (3.1)	5 (4.8)
Gastroenteritis	1 (2.7)	3 (4.5)	4 (5.6)	0	4 (3.8)
Pneumonia	2 (5.4)	1 (1.5)	3 (4.2)	0	3 (2.9)
Sinusitis	0	2 (3.0)	0	2 (6.3)	2 (1.9)
Nervous system disorders	**7 (18.9)**	**18 (26.9)**	**19 (26.4)**	**6 (18.8)**	**25 (24.0)**
Headache	4 (10.8)	13 (19.4)	13 (18.1)	4 (12.5)	17 (16.3)
Dizziness	2 (5.4)	4 (6.0)	5 (6.9)	1 (3.1)	6 (5.8)
Psychiatric disorders	**9 (24.3)**	**14 (20.9)**	**17 (23.6)**	**6 (18.8)**	**23 (22.1)**
Nightmare	3 (8.1)	1 (1.5)	2 (2.8)	2 (6.3)	4 (3.8)
Somnambulism	2 (5.4)	2 (3.0)	4 (5.6)	0	4 (3.8)
Confusional arousal	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Anxiety	2 (5.4)	0	2 (2.8)	0	2 (1.9)
Renal and urinary disorders	**7 (18.9)**	**14 (20.9)**	**17 (23.6)**	**4 (12.5)**	**21 (20.2)**
Enuresis	7 (18.9)	12 (17.9)	15 (20.8)	4 (12.5)	19 (18.3)
Investigations	**9 (24.3)**	**9 (13.4)**	**14 (19.4)**	**4 (12.5)**	**18 (17.3)**
Weight decreased	5 (13.5)	7 (10.4)	11 (15.3)	1 (3.1)	12 (11.5)
Respiratory, thoracic and mediastinal disorders	**6 (16.2)**	**7 (10.4)**	**9 (12.5)**	**4 (12.5)**	**13 (12.5)**
Cough	2 (5.4)	2 (3.0)	2 (2.8)	2 (6.3)	4 (3.8)

System Organ Class Preferred Term	Age[a] (years) 7 to 11 N = 37	 12 to 17 N = 67	Xyrem Status at Study Entry Xyrem Naïve N = 72	 On Xyrem N = 32	Total N = 104
Nasal congestion	3 (8.1)	1 (1.5)	4 (5.6)	0	4 (3.8)
Oropharyngeal pain	0	2 (3.0)	0	2 (6.3)	2 (1.9)
Injury, poisoning and procedural complications	**5 (13.5)**	**6 (9.0)**	**6 (8.3)**	**5 (15.6)**	**11 (10.6)**
Contusion	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Procedural pain	1 (2.7)	2 (3.0)	1 (1.4)	2 (6.3)	3 (2.9)
Metabolism and nutrition disorders	**3 (8.1)**	**8 (11.9)**	**11 (15.3)**	**0**	**11 (10.6)**
Decreased appetite	2 (5.4)	6 (9.0)	8 (11.1)	0	8 (7.7)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in subjects who received Placebo during the Double-Blind Treatment Period.
Note: Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: Subjects may have more than one event with the same SOC. They are counted once in the SOC summary. Subjects may have more than one event with the same PT. They are counted once in the PT summary.
Note: Some SOCs may have achieved the 5% threshold, but if no underlying PTs achieved the 5% threshold, the SOC is not displayed.
[a] Age in years at the first dispensation of study drug.
MedDRA version 17.0.

An overall summary of adverse events that occurred during the double-blind randomized withdrawal period is in the next table taken from the submission and is self-explanatory. Adverse event data for patients who were not randomized but continued to take open-label Xyrem® during that period are also summarized in the table below.

	Treatment Received Randomized Placebo N = 32	 Randomized Xyrem N = 31	 Open-label Xyrem[a] N = 32	 All Xyrem N = 63	Total N = 95
Any TEAEs	**10 (31.3)**	**5 (16.1)**	**5 (15.6)**	**10 (15.9)**	**20 (21.1)**
Any Related TEAEs[b]	7 (21.9)	3 (9.7)	1 (3.1)	4 (6.3)	11 (11.6)
Any TEAEs Leading to Drug Interruption	0	0	1 (3.1)	1 (1.6)	1 (1.1)
Any TEAEs Leading to Drug Withdrawal	0	0	1 (3.1)	1 (1.6)	1 (1.1)
Any Severe TEAEs	0	0	0	0	0
Any Serious TEAEs	0	0	0	0	0
Any Fatal TEAEs	0	0	0	0	0
Any TEAEs of Special Interest	7 (21.9)	2 (6.5)	1 (3.1)	3 (4.8)	10 (10.5)

Abbreviations: TEAE = treatment emergent adverse event
Note: Events with onset on or after the first dose in the Double-blind Treatment Period and prior to the date of first dose in the Open-label Safety Period are presented. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
[a] Subjects entering the Double-blind Treatment Period after the DSMB recommendation to end placebo treatment received open-label Xyrem during this 2-week Treatment Period.
[b] Related TEAEs included events considered by the Investigator to be related or suspected to be related to study drug.

A summary of all adverse events that occurred during the double-blind randomized withdrawal period is in the next table copied from the submission and is self-explanatory. Adverse event data for patients who were not randomized but continued to take open-label Xyrem® during that period are also summarized in the table below. Not surprisingly, in the randomized patients, the incidence of somnolence and cataplexy (as adverse events) was much higher in those who were randomized to placebo than in those randomized to Xyrem®.

	Treatment Received				
	Randomized Placebo N = 32	Randomized Xyrem N = 31	Open-label Xyrem[a] N = 32	All Xyrem N = 63	Total N = 95
Any TEAEs	**10 (31.3)**	**5 (16.1)**	**5 (15.6)**	**10 (15.9)**	**20 (21.1)**
Nervous System Disorders	**7 (21.9)**	**0**	**1 (3.1)**	**1 (1.6)**	**8 (8.4)**
Somnolence	7 (21.9)	0	0	0	7 (7.4)
Cataplexy	6 (18.8)	0	0	0	6 (6.3)
Psychiatric Disorders	**5 (15.6)**	**2 (6.5)**	**0**	**2 (3.2)**	**7 (7.4)**
Sleep disorder	2 (6.3)	1 (3.2)	0	1 (1.6)	3 (3.2)
Skin and Subcutaneous Tissue Disorders	**0**	**2 (6.5)**	**0**	**2 (3.2)**	**2 (2.1)**
Pruritus	0	2 (6.5)	0	2 (3.2)	2 (2.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment emergent adverse event
Note: Events with onset on or after the first dose in the Double-blind Treatment Period and prior to the date of first dose in the Open-label Safety Period are presented. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: Subjects may have more than one event with the same SOC; they are counted once in the SOC summary. Subjects may have more than one event with the same PT; they are counted once in the PT summary. SOCs are sorted in descending order of total incidence. PTs within SOC are sorted in descending order of incidence.
Note: Some SOCs may have achieved the 5% threshold, but if no underlying PTs achieved the 5% threshold, the SOC is not displayed.
[a] Subjects entering the Double-blind Treatment Period after the DSMB recommendation to end placebo treatment received open-label Xyrem during this 2-week Treatment Period.
MedDRA Version 17.0.

The incidence of adverse events (reported in ≥ 5% of subjects in each age group and prior Xyrem®-status category) that occurred during the titration, stable dose, and open-label safety periods has also been summarized by the sponsor in separate tables in the submission, but those data have been subsumed under a similar table covering the entire study that is already in the earlier part of this section.

Adverse events of special interest across all study periods in patients receiving Xyrem® and in the safety population are summarized in the next table. The findings in that table are not distinct from those elsewhere in this study report.

	Age (years)[a]		Xyrem Status at Study Entry		Total
	7 to 11 N = 37	12 to 17 N = 67	Xyrem Naïve N = 72	On Xyrem N = 32	N = 104
Any TEAEs of Special Interest	**13 (35.1)**	**17 (25.4)**	**24 (33.3)**	**6 (18.8)**	**30 (28.8)**
Psychiatric disorders	**8 (21.6)**	**11 (16.4)**	**15 (20.8)**	**4 (12.5)**	**19 (18.3)**
Nightmare	3 (8.1)	1 (1.5)	2 (2.8)	2 (6.3)	4 (3.8)
Somnambulism	2 (5.4)	2 (3.0)	4 (5.6)	0	4 (3.8)
Confusional arousal	2 (5.4)	1 (1.5)	2 (2.8)	1 (3.1)	3 (2.9)
Anxiety	2 (5.4)	0	2 (2.8)	0	2 (1.9)
Acute psychosis	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Affect lability	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Confusional state	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Irritability	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Mental status changes	0	1 (1.5)	0	1 (3.1)	1 (1.0)
Mood altered	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Stress	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Suicidal ideation	0	1 (1.5)	1 (1.4)	0	1 (1.0)
Investigations	**5 (13.5)**	**7 (10.4)**	**11 (15.3)**	**1 (3.1)**	**12 (11.5)**
Weight decreased	5 (13.5)	7 (10.4)	11 (15.3)	1 (3.1)	12 (11.5)
Nervous system disorders	**1 (2.7)**	**1 (1.5)**	**2 (2.8)**	**0**	**2 (1.9)**
Somnolence	1 (2.7)	1 (1.5)	2 (2.8)	0	2 (1.9)
Respiratory, thoracic and mediastinal disorders	**1 (2.7)**	**1 (1.5)**	**1 (1.4)**	**1 (3.1)**	**2 (1.9)**
Sleep apnoea syndrome	1 (2.7)	1 (1.5)	1 (1.4)	1 (3.1)	2 (1.9)
General disorders and administration site conditions	**0**	**1 (1.5)**	**1 (1.4)**	**0**	**1 (1.0)**
Feeling jittery	0	1 (1.5)	1 (1.4)	0	1 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment emergent adverse event
[a] Age in years at the first dispensation of study drug.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in subjects who received Placebo during the Double-blind Treatment Period.
Note: Events with onset > 30 days after the last dose of study drug in the study were excluded. Subjects with more than one event with the same SOC are counted once in the SOC summary. Subjects with more than one event with the same PT are counted once in the PT summary.
MedDRA Version 17.0.

Further analyses of each of the events in the above table have been presented by the sponsor, but do not reveal any information that is unexpected or distinctive for children.

6.5.11.3 Safety Laboratory Tests

There are no items of concern in the sponsor's display and analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during this study.

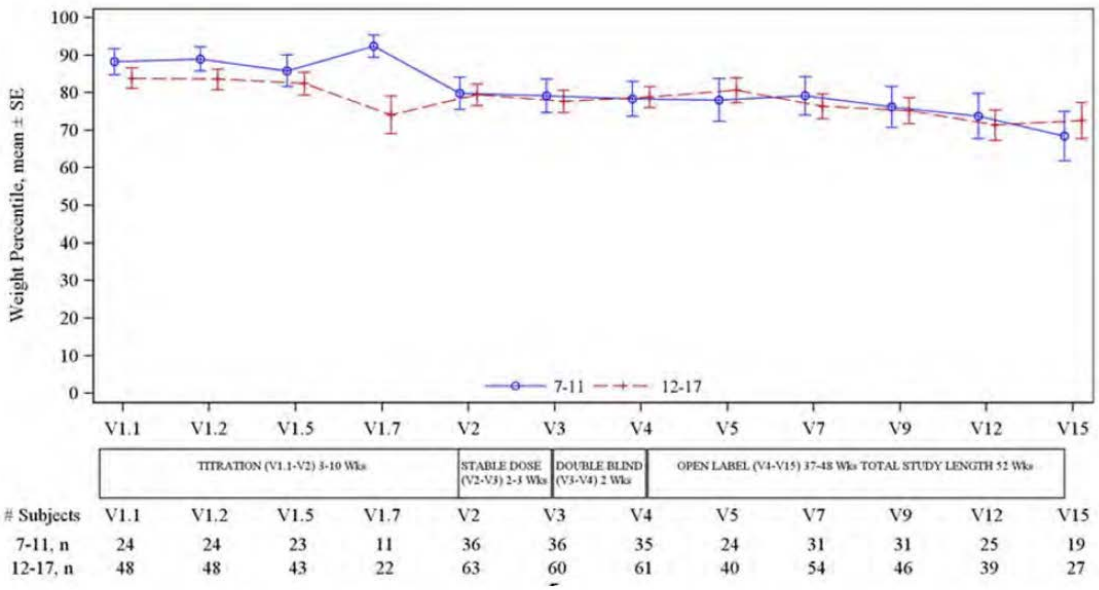
The analysis of growth hormone, insulin-like growth factor 1, and prolactin concentrations obtained over the course of the study revealed no data of significance; neither did the analysis of measures of precocious puberty (luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, and Tanner staging) conducted in girls < 8 years old and boys < 9 years old.

6.5.11.4 Vital Signs, Height, Weight, And Body Mass Index

The changes observed in blood pressure, pulse rate, respiratory rate, and temperature during this study were unremarkable and did not appear to be of clinical significance.

No effect of Xyrem® on height were observed during the study.

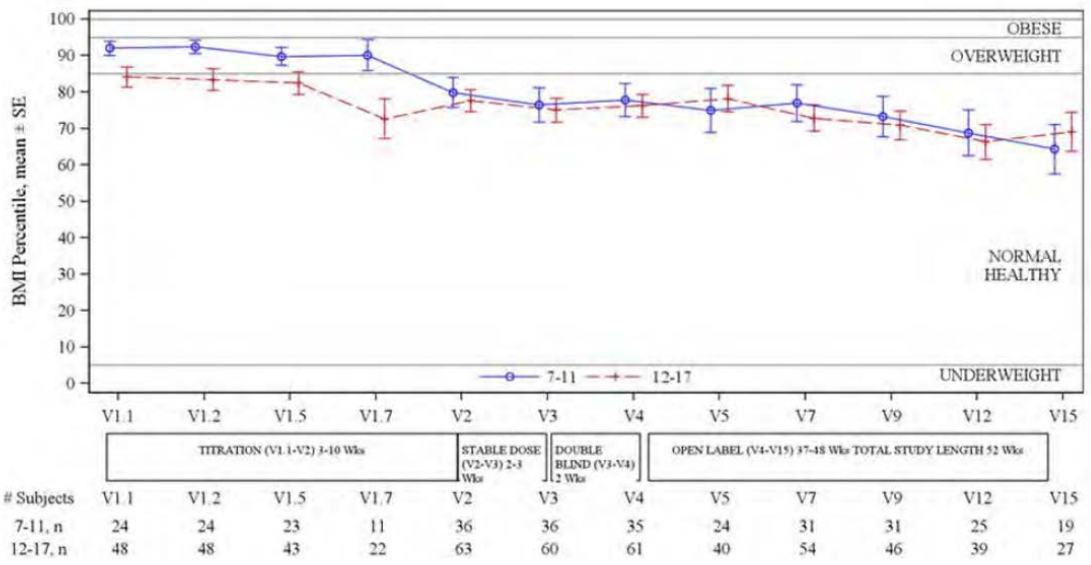
Mean body weight percentile demonstrated a slight decrease over the course of this study. Mean body weight percentile by time data by age category is in the following figure for the safety population which I have taken from the submission.



# Subjects	V1.1	V1.2	V1.5	V1.7	V2	V3	V4	V5	V7	V9	V12	V15
7-11, n	24	24	23	11	36	36	35	24	31	31	25	19
12-17, n	48	48	43	22	63	60	61	40	54	46	39	27

Note: The Safety Population consists of all subjects who were dispensed study drug. Time between visits is not equally spaced. The error bars represent mean - 1 SE to mean + 1 SE.

A trend to a decrease in body mass index percentile was also observed during this study, that was similar for both age-group categories as displayed in the next sponsor figure. The next figure displays body mass index percentile over time in the safety population in both age categories.



# Subjects	V1.1	V1.2	V1.5	V1.7	V2	V3	V4	V5	V7	V9	V12	V15
7-11, n	24	24	23	11	36	36	35	24	31	31	25	19
12-17, n	48	48	43	22	63	60	61	40	54	46	39	27

Note: The Safety Population consists of all subjects who were dispensed study drug. Time between visits is not equally spaced. The error bars represent mean - 1 SE to mean + 1 SE. BMI values less than the 5th percentile are classified as underweight, values between 85 to < 95 are classified as overweight, and values ≥ 95 are classified as obese.

6.5.11.5 Electrocardiograms

No clinically significant findings were noted in the sponsor's analysis of electrocardiographic data obtained during this study.

6.5.11.6 Polysomnograms

No clinically-significant changes in polysomnographic measures of central or obstructive sleep apnea and hypopnea, or oxygen desaturation were seen in this study as is displayed in the following sponsor tables.

Respiratory Parameters Collected during Full Night PSG for Subject who were Xyrem Naïve at Study Entry

Parameters	Screening PSG (without Xyrem) N = 73	End of Stable Dose PSG (with Xyrem) N = 64	Change from Screening – End of Stable Dose N = 63	End of Study PSG (with Xyrem) N = 30	Change from Screening - EoS N = 30	Change from End of Stable Dose - EoS N = 30
			Mean (SD); Median (Q1, Q3)			
Apnea + Hypoapnea index	1.24 (1.180) 1 (0.40, 1.70)	1.924 (4.8115) 1.1 (0.4, 1.65)	0.652 (4.9763) -0.1 (-0.8, 0.6)	0.787 (0.7763) 0.55 (0.3, 0.8)	-0.663 (1.1857) -0.70 (-1.4, 0)	-0.675 (1.6908) -0.20 (-0.960, 0.300)
Apnea index	0.31 (0.483) 0.10 (0.00, 0.40)	1.155 (4.6975) 0.3 (0, 0.7)	0.853(4.7606) 0 (-0.1, 0.3)	0.380 (0.4937) 0 (0, 0.5)	-0.023 (0.6431) 0 (-0.2, 0.2)	-0.0292 (1.5189) 0 (-0.5, 0.2)
Central apnea index	0.27 (0.452) 0.1 (0, 0.40)	1.123 (4.6531) 0.3 (0, 0.675)	0.864 (4.7214) 0 (-0.1, 0.3)	0.293 (0.3732) 0.2 (0, 0.4)	-0.8 (0.6386) 0 (-0.3, 0.1)	-0.338 (1.4855) -0.1 (-0.4, 0.1)
Obstructive apnea + hypoapnea index	0.95 (0.937) 0.7 (0.30, 1.20)	0.797 (0.8989) 0.45 (0.1, 1.150)	-0.205 (0.9494) -0.2 (-0.7, 0.2)	0.473 (0.6373) 0.3 (0.1, 0.6)	-0.59 (0.8953) -0.55 (-1.1, 0)	-0.347 (0.8287) -0.2 (-0.7, 0.1)
Obstructive index	0.03 (0.088) 0 (0, 0)	0.03 (0.092) 0 (0, 0)	-0.01 (0.111) 0 (0, 0)	0.08 (0.315) 0 (0, 0)	0.06 (0.309) 0 (0, 0)	0.05 (0.264) 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0 (0); 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0.018) 0 (0, 0)
Percent TST with SpO_2 < 90%	0.00 (0.026) 0 (0, 0)	0.03 (0.167) 0 (0, 0)	0.02 (0.171) 0 (0, 0)	0.01 (0.025) 0 (0, 0)	0 (0.032) 0 (0, 0)	-0.01 (0.066) 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (mins)	0 (0) 0 (0, 0)	0.01 (0.072) 0 (0, 0)	0.01 (0.073) 0 (0, 0)	0 (0.018) 0 (0, 0)	0 (0.018) 0 (0, 0)	-0.01 (0.058) 0 (0, 0)
Total time SpO_2 is < 90% during TST (mins)	0.03 (0.140) 0 (0, 0)	0.13 (0.826) 0 (0, 0)	0.10 (0.851) 0 (0, 0)	0.03 (0.102) 0 (0, 0)	0.01 (0.118) 0 (0, 0)	-0.03 (0.268) 0 (0, 0)
Mean SpO_2 during TST (%)	97.40 (0.944) 97.3 (96.80, 98.00)	97.09 (0.998) 97.1 (96.40, 97.75)	-0.25 (0.917) -0.3 (-0.80, 0.30)	97.41 (0.937) 97.25 (96.90, 97.90)	-0.12 (1.183) 0.05 (-1.0, 0.20)	0.26 (1.150) 0.15 (-0.2, 0.50)

Abbreviations: EoS = end of study; Max = maximum; Min = minimum; mins = minutes; PSG = polysomnogram; SpO_2 = oxygen saturation; TST = total sleep time.

Respiratory Parameters Collected during Full Night PSG for Subjects on Xyrem at Study Entry

Parameters	Screening PSG (with Xyrem) N = 32	End of Study PSG (with Xyrem) N = 17	Change from Screening – EoS N = 17
		Mean (SD); Median (Q1, Q3)	
Apnea + Hypoapnea index	1.16 (1.269); 0.85 (0.25, 1.65)	3.48 (7.187); 0.8 (0.20, 1.80)	1.85 (6.818); -0.1 (-0.90, 0.60)
Apnea index	0.44 (0.750); 0.1 (0.0, 0.65)	2.11 (4.535); 0.3 (0.0, 0.60)	1.51 (4.380); 0 (0.0, 0.60)
Central apnea index	0.42 (0.72); 0.1 (0, 0.65)	1.94 (4.287); 0.1 (0.0, 0.60)	1.36 (4.116); 0 (-0.10, 0.60)
Obstructive apnea + hypoapnea index	0.73 (0.796); 0.45 (0.15, 1.05)	1.53 (4.21); 0.4 (0.0, 1.40)	0.49 (3.732); -0.4 (-0.90, 0.20)
Obstructive index	0.02 (0.072); 0 (0, 0)	0.16 (0.557); 0 (0, 0)	0.15 (0.556); 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0.01 (0.071); 0(0, 0)	0.02 (0.073); 0 (0, 0)	-0.01 (0.125); 0 (0, 0)
Percent TST with SpO_2 < 90%	0.09 (0.512); 0 (0, 0)	0.18 (0.517); 0 (0, 0)	0.01 (0.910); 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (mins)	0.06 (0.336); 0(0, 0)	0.09 (0.363); 0 (0, 0)	0.02 (0.605); 0 (0, 0)
Total time SpO_2 is < 90% during TST (mins)	0.46 (2.562); 0 (0, 0)	0.78 (2.182); 0 (0, 0)	-0.07 (4.306); 0 (0, 0)
Mean SpO_2 during TST (%)	97.52 (0.828); 97.5 (96.95, 98.20)	97.25 (1.154); 97.2 (96.60, 98.10)	-0.28 (1.048) -0.20 (-0.90, 0.30)

Abbreviations: EoS = end of study; Max = maximum; Min = minimum; mins = minutes; PSG = polysomnogram; SpO_2 = oxygen saturation; TST = total sleep time.

Additional analyses and descriptions of individual patients reported to have arterial oxygen desaturation do not reveal any data of concern.

6.5.11.7 Columbia-Suicide Severity Rating Scale, Children's Depression Inventory, And Multidimensional Anxiety Scale For Children-10

Among subjects who took Xyrem®, two subjects responded positively to the Columbia-Suicide Severity Rating Scale. Those were the 2 subjects with serious adverse events for whom narratives have been provided earlier and are listed in the following table. A further description of those patients is not warranted.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Severe
13 / Male / White		*Acute Psychosis*		Recovered / Resolved
(b) (6)	Dose Titration Period	Psychiatric Disorders	Related	Moderate
14 / Male / White		*Suicidal ideation*		Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

A slight downward trend in mean Children's Depression Inventory T-scores in both Xyrem® naïve and Xyrem®-treated subjects was observed during the course of the study (higher scores correlate with more severe depression). Scores, however, remained within the average range.

Scores on the Multidimensional Anxiety Scale for Children-10 remained steady during the study.

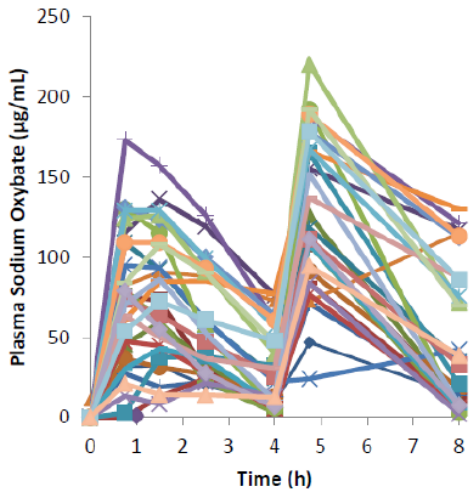
6.5.12 Pharmacokinetic Results

Pharmacokinetic results for this study came from the pharmacokinetic completer population comprising 29 patients and included 11 patients in the 7 to 11 year age group and 18 patients in the 12 to 17 year age group.

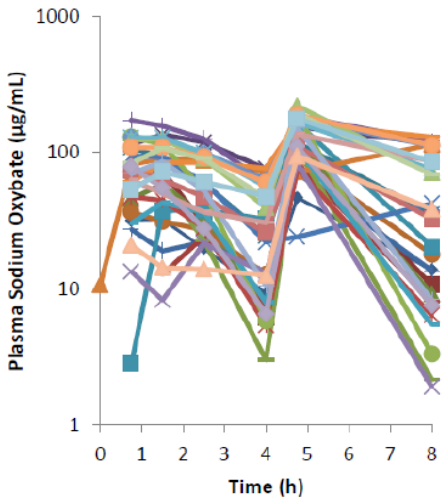
Plasma sodium oxybate concentration-time profiles (using linear and log-linear scales) after the administration of Xyrem® at the full and stable dose in this study is revealed in the following sponsor figure. The profiles represent changes after the first and second nightly doses during the second pharmacokinetic night.

Plasma Sodium Oxybate Concentration-time Profiles for Individual Subjects following Administration of Xyrem during PK Night 2 (PK Population)

A. Linear Scale



B. Log-linear Scale



The plots correspond to Xyrem doses ranging from 4 to 9 grams per night. Xyrem was administered as 2 evenly divided doses (first and second nightly doses) given 4 hours apart.

Sodium oxybate pharmacokinetic parameters for the first nightly dose of Xyrem® are in the following sponsor table.

First Nightly Dose (g)[a]	Number of Subjects	T_{max} (hours)[a] (Median [Min, Max])	C_{max} (µg/mL) (Mean [CV%])	AUC_{0-4h} (µg/mL*hours) (Mean [CV%])
2	1	0.75 (NC)	79.4 (NC)	143 (NC)
2.25	3	0.82 (0.75-1.50)	72.5 (73%)	195 (83%)
2.5	2	1.66 (0.82-2.50)	65.3 (95%)	156 (92%)
3	1	2.47 (NC)	24.3 (NC)	52.0 (NC)
3.25	3	0.75 (0.75-2.50)	92.5 (36%)	273 (40%)
3.5	8	1.50 (0.75-1.50)	82.9 (60%)	234 (62%)
3.75	3	0.75 (0.75-1.48)	92.7 (35%)	214 (25%)
4	4	0.75 (0.75-1.50)	84.1 (44%)	209 (53%)
4.25	1	0.75 (NC)	47.4 (NC)	114 (NC)
4.5	3	1.50 (0.75-2.50)	82.4 (60%)	233 (67%)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; C_{max} = maximum observed plasma concentration; NC = not calculated since only one observation available; T_{max} = time of maximum observed plasma concentration.
[a] Based on half of the planned full nightly dose (Xyrem dosage, g/night).
Note: Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.
Note: For T_{max}, median values are reported and the range of observed values (minimum-maximum) are reported in parentheses. For C_{max} and AUC_{0-4h}, mean values are reported and the coefficients of variation (SD / mean expressed as a percentage) are shown in parentheses.

Sodium oxybate pharmacokinetic parameters for the second nightly dose of Xyrem® are in the next sponsor table.

Nightly Dose (g), BID	Number of Subjects	$C_{4.75h}$ (µg/mL) (Mean [CV%])	C_{8h} (µg/mL) (Mean [CV%])
2	1	108 (NC)	2.16 (NC)
2.25	3	125 (43%)	44.9 (129%)
2.5	2	101 (24%)	18.6 (127%)
3	1	83.6 (NC)	8.13 (NC)
3.25	3	157 (11%)	97.5 (29%)
3.5	8	130 (44%)	60.6 (83%)
3.75	3	159 (28%)	33.3 (137%)
4	4	112 (73%)	34.8 (82%)
4.25	1	76.7 (NC)	6.40 (NC)
4.5	3	144 (20%)	56.7 (93%)

Abbreviations: C4.75h = plasma concentration at 4.75 hours postdose; C8h = plasma concentration at 8 hours; NC = not calculated due to only one observation; BID= two times a night.
Results are presented for PK Night 2, on which subjects received their full stable dose of Xyrem.
Mean values are reported the coefficients of variation (SD/mean expressed as a percentage) are shown in parentheses.

The dose proportionality assessment is summarized in the next table from the submission, the footnotes to the table explain that assessment. The sponsor has concluded that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

	C_{max}	AUC_{0-4h}
Ratio	1.97	2.53
(90% CI)	(1.67 – 2.31)	(2.18 – 2.94)

Abbreviations: AUC_{0-4h} = area under the plasma concentration-time curve from time zero to 4 hours postdose; CI = confidence interval; C_{max} = maximum observed plasma concentration.
Note: Ratio and confidence interval obtained from a normal distribution and confidence interval for natural log (value on PK Night 2) – natural log (value on PK Night 1). The mean of the difference in logs and confidence intervals are back-transformed to ratio scale.
Note: As described in the text, half of the stable dose was taken on PK night 1, and the full stable dose was taken on PK night 2; therefore, a ratio of 2.00 signifies dose proportionality.

The sponsor has also compared pharmacokinetic data obtained in children with historical pharmacokinetic obtained in adults: while the major pharmacokinetic attributes in children were similar to those obtained in adults, there was greater variability in plasma pharmacokinetic exposure parameters in children.

6.6 Sponsor's Conclusions

The sponsor has drawn the following salient conclusions from the results of Study 13-005.

- Xyrem® had efficacy in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in pediatric subjects.
- The safety profile of Xyrem® in pediatric subjects was similar to that observed in adults.
- The pharmacokinetics of Xyrem® in children were collectively similar to those seen in adults.

6.7 Reviewer's Summary Comments

6.7.1 Study Design And Significant Amendments

Protocol 13-005 had the following main features:

- The primary objectives of the study were to evaluate the efficacy and safety of Xyrem® in the treatment of pediatric patients (aged 7 to 17 years) who have narcolepsy with cataplexy

- This study had a number of consecutive segments, of which the main randomized, double-blind, placebo-controlled, parallel-arm withdrawal segment was to be the component of the study directed at evaluating the efficacy of Xyrem® in the treatment of cataplexy associated with narcolepsy in children.

- About 100 patients aged 7 to 16 years at study entry were to be enrolled. They would be either Xyrem®-naïve or taking a stable dose of Xyrem® (and a stable dose of stimulants for narcolepsy, if applicable) for at least 2 months prior to study entry. Other key inclusion criteria were as follows: primary diagnosis of narcolepsy with cataplexy meeting International Classification of Sleep Disorders (ICSD)-2 criteria or ICSD-3 criteria, whichever was in effect at the time of the study; positive for the HLA DQB1:0602 haplotype; and history of at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness prior to beginning any narcolepsy treatment.

- Throughout the study, all nightly doses of Xyrem® and placebo were to be administered in 2 divided doses, administered 2.5 to 4 hours apart. The starting and maximum doses of Xyrem® as well as the Xyrem® titration regimen (if required) were to be determined based on body weight stratum.

- The consecutive segments of this study were as follows:

    - A screening period lasting up to 30 days.

    - A 3 to 10 week open-label titration period lasting 3 to 10 weeks for patients who were Xyrem®-naïve at study entry.

    - An open-label stable-dose period lasting 2 to 3 weeks. During this phase, a subset of about 24 patients (completers) who were taking a stable dose of Xyrem® at study entry were to participate in an open-label evaluation of the pharmacokinetics of Xyrem®.

    - A double-blind, placebo-controlled withdrawal phase lasting 2 weeks during which period patients were randomized 1:1 to treatment either with Xyrem® in the stable dose established during the preceding 2 weeks or placebo.

    - An open-label safety component which allowed for a total exposure to Xyrem® of up to 1 year.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks during the 2 weeks of the double-blind period, compared with the last 2 weeks of the stable-dose period.

- Key secondary efficacy parameters were the following:

    - Clinical Global Impression of Change for cataplexy severity, comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in the modified Epworth Sleepiness Scale (modified for children and adolescents) score from the end of the stable-dose period to the end of the double-blind period.

- Other secondary efficacy parameters were the following

    - Clinical Global Impression of Change for narcolepsy severity overall comparing the end of the double-blind period with the end of the stable-dose period.

    - Change in quality of life (based on the Short Form-10) from the end of the stable-dose period to the end of the double-blind period.

- Safety monitoring was to comprise assessment of the following during the course of the study: adverse events, vital signs, height, weight, physical examinations, 12-lead electrocardiograms, polysomnographic parameters (including measures of respiration), safety laboratory tests, assessments of growth and precocious puberty (including growth hormone levels), Columbia-Suicide Severity Rating Scale, Children's Depression Inventory 2nd Edition Self-Report Short Version, and Multidimensional Anxiety Scale for Children 10-item Anxiety Index.

- Plasma concentrations of sodium oxybate were measured in the subset of patients participating in the pharmacokinetic analysis, and various pharmacokinetic parameters derived from those data and analyzed further.

- A tiered analysis of the efficacy parameters was conducted beginning with the primary efficacy parameter followed by the two key secondary efficacy parameters (with the Clinical Global Impression of Change in cataplexy severity analyzed first and the change in modified Epworth Sleepiness Scale score analyzed later), and finally the two other secondary efficacy parameters in the same order as stated above.

A pre-specified interim efficacy analysis (on the primary efficacy endpoint) for this protocol that was conducted after 35 subjects completed or discontinued early from the double-blind treatment period led to the Data Safety Monitoring Board for Study 13-005 concluding that Xyrem had demonstrated efficacy in the treatment of cataplexy (it had demonstrated that Xyrem was superior to placebo in the treatment of cataplexy at a p-value ≤ 0.005): the Board then recommended that the double-blind segment of Study 13-005 be discontinued, while the open-label extension (including pharmacokinetic evaluation) continue. The Data Safety Monitoring Board for Study 13-005 also recommended that patients continue to be enrolled in the open-label pharmacokinetic segment.

The pediatric Written Request under which Study 13-005 was first conducted was amended after the pre-specified interim analysis led to a protocol amendment. The study protocol was also amended to allow for the duration of the open-label safety component to be further extended so that the total duration of Xyrem® treatment for an individual patient could extend up to 3 years; the part of the study originally proposed was then referred to as Part 1 with the newly-proposed extension as Part 2.

6.7.2 Study Results

Study 13-005 was conducted in a manner consistent with the study protocol.

A total of 106 patients were enrolled in this study of whom 104 appear to have received study drug. 99 patients entered the stable-dose period, with 96 of those patients completing that period. Of the 96 patients who completed the stable-dose period, 63 patients participated in the randomized, double-blind, withdrawal phase of the study, whereas the remaining 33 patients continued to take open-label Xyrem. 95 patients then entered the open-label safety period of the study. As of the cut-off date for the 120-day safety update, 85 patients had completed Part 1 of the study and 44 patients had entered Part 2.

During the randomized, double-blind, withdrawal phase, 31 patients were assigned to Xyrem® (30 patients completed that phase) and 32 patients were assigned to placebo (all 32 patients completed that phase).

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two -week randomized withdrawal period in the weekly number of cataplexy attacks was 17.37 for the placebo group and 2.52 for the group that continued to take Xyrem® (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring Xyrem® over placebo were seen on the two key secondary efficacy parameters analyzed in the prespecified sequence, the Clinical Global Impression of Change for Cataplexy Severity ($p = 0.0006$) and the change from baseline in modified Epworth Sleepiness Scale score ($p = 0.0001$).

The adverse event profile of Xyrem® seen in this study was not substantially different from that seen in adults. The other safety outcomes did not reveal any data of concern.

The pharmacokinetic completer population consisted of 29 patients, of whom 11 were aged 7 to 11 years, and 18 were aged 12 to 17 years. These data revealed a pharmacokinetic profile for Xyrem® in children that was similar to that seen in adults. A dose-proportionality assessment indicated that while the C_{max} was dose-proportional, the AUC_{0-4} was supra-dose-proportional.

7. 120-Day Safety Update

The 120-Day Safety Update for this sNDA was submitted on August 23, 2018.

This Update contains safety data from Parts 1 and 2 of Study 13-005, with a cut-off date of April 30, 2018. (The cut-off date for safety data in the original submission of this sNDA was February 10, 2017).

The safety data included in this update are cumulative for Study 13-005. The data in this update are summarized under the following headings.

7.1 Exposure

As of April 30, 2018, 104 subjects had received Xyrem® for a median duration of 370 days (range: 352 to 492 days) in this study. The distribution of that exposure by duration categories and by cumulative Xyrem® dosage is summarized in the following sponsor table, which is for the safety population.

	Total N = 106
Duration of Xyrem usage (days)[a]	
n	104
Mean (SD)	392.4 (159.77)
Median	370.0
Q1, Q3	352.0, 492.0
Categorized Duration of Study Drug usage	
≥ 6 months	91 (85.8)
≥ 1 year	76 (71.7)
≥ 18 months	20 (18.9)
Cumulative Xyrem dosage received (g)[b]	
n	104
Mean (SD)	2624.355 (1304.8288)
Median	2600.250
Q1, Q3	1807.500, 3690.500

Abbreviations: N = the total number of subjects in the population; n = number of subjects observed; Q1 = first quartile; Q3 = third quartile.

[a] For subjects who received Xyrem during the Double-blind Treatment Period, this duration will be the same as the Total Duration of Dosing. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equals the Total Duration of Dosing over Part 1 and Part 2 minus Duration of Treatment during the Double-blind Treatment Period.

[b] For subjects who received Xyrem during the Double-blind Treatment Period, this is the cumulative dosage (based on the assigned dosage by the investigator and assuming the subject took the complete assigned dosage every night) used over all periods of study drug exposure. For subjects who received Placebo during the Double-blind Treatment Period, this is the cumulative dosage used over all periods of study drug exposure minus the cumulative dosage used during the Double-blind Treatment Period.

Note: Percentages are calculated using the number of subjects with a duration value in the column.

Note: The Safety Population consists of all subjects who were dispensed study drug.

The duration of Xyrem® use at the maximum nightly dose by age group and weight category at study entry is summarized in the next sponsor table, which is for the safety population.

Subject Weight at Baseline [a]	Maximum Total Nightly Dose	Statistic	Age 7 to 11 [b] N = 37	Age 12 to 17 [b] N = 67	Total N = 104
Xyrem naïve at Study Entry		M [c]	24	48	72
< 30 kg	**6 g/night**	m [c]	2	0	2
		n/m(%) [c]	0/2 (0)	0	0/2 (0)
30 to < 45 kg	**7.5 g/night**	m [c]	9	1	10
		n/m(%) [c]	2/9 (22.2)	0/1 (0)	2/10 (20.0)
		Exposure Days			
		n	2	0	2
		Mean (SD)	262.5 (212.84)	NA	262.5 (212.84)
		Median	262.5	NA	262.5
		Q1, Q3	112.0, 413.0	NA	112.0, 413.0
≥ 45 kg	**9 g/night**	m [c]	13	47	60
		n/m(%) [c]	4/13 (30.8)	14/47 (29.8)	18/60 (30.0)
		Exposure Days			
		n	4	14	18
		Mean (SD)	134.3 (122.00)	307.9 (172.57)	269.3 (175.84)
		Median	128.0	339.0	285.0
		Q1, Q3	32.5, 236.0	143.0, 429.0	85.0, 424.0
On Xyrem at Study Entry		M [c]	13	19	32
< 30 kg	**6 g/night**	m [c]	3	0	3
		n/m(%) [c]	3/3 (100.0)	0	3/3 (100.0)
		Exposure Days			
		n	3	0	3
		Mean (SD)	423.0 (316.31)	NA	423.0 (316.31)
		Median	594.0	NA	594.0
		Q1, Q3	58.0, 617.0	NA	58.0, 617.0
30 to < 45 kg	**7.5g/night**	m [c]	5	1	6
		n/m(%) [c]	1/5 (20.0)	0/1 (0)	1/6 (16.7)
		Exposure Days			
		n	1	0	1
		Mean (SD)	366.0 (NC)	NA	366.0 (NC)
		Median	366.0	NA	366.0
		Q1, Q3	366.0, 366.0	NA	366.0, 366.0

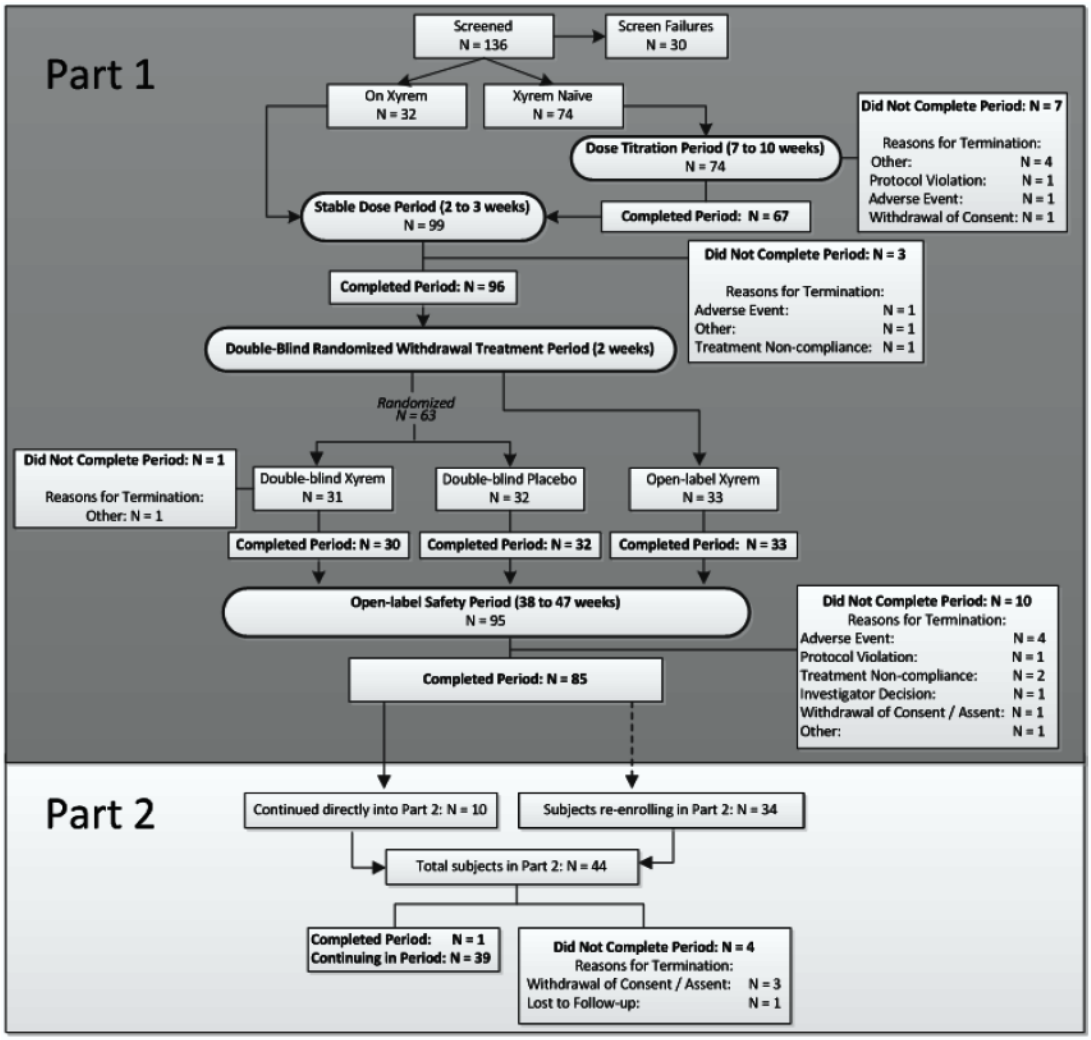
Subject Weight at Baseline [a]	Maximum Total Nightly Dose	Statistic	Age 7 to 11 [b] N = 37	Age 12 to 17 [b] N = 67	Total N = 104
≥ 45 kg	9 g/night	m [c]	5	18	23
		n/m(%) [c]	0/5 (0)	1/18 (5.6)	1/23 (4.3)
		Exposure Days			
		n	0	1	1
		Mean (SD)	NA	411.0 (NC)	411.0 (NC)
		Median	NA	411.0	411.0
		Q1, Q3	NA	411.0, 411.0	411.0, 411.0

Abbreviations: N = the total number of subjects in the population; NC = not calculated; NA = not available; Q1 = first quartile; Q3 = third quartile.
[a] Baseline weight (kg) refers to the last non-missing value collected prior to or on study Day 1.
[b] Age in years at the first dispense of study drug in Part 1.
[c] M: the number of subjects by each age group and Xyrem status at study entry; m: the number of subjects by each age group, Xyrem status at study entry and weight group; n: the number of subjects by each age group, Xyrem status at study entry, weight group, and met the total maximum nightly Xyrem dose at anytime during the study.
Note: The Safety Population consists of all subjects who were dispensed study drug.
Per protocol, the maximum total nightly dose by weight was only specified for Xyrem naïve subjects and does not apply to on Xyrem subjects. For subjects who received Placebo during the Double-blind Treatment Period, Total Duration of Xyrem Usage equals the Total Duration of Dosing minus Duration of Treatment during the Double-blind Treatment Period.
One subject (b) (6) who was on Xyrem at study entry had a dose that exceeded the maximum total nightly dose in the study allowed for Xyrem-naïve subjects. The subject was < 30 kg at study entry and received a dose of 7.5 g/night.

7.2 Disposition

By April 30, 2018, 85 patients had completed Part 1 and 44 patients were enrolled in Part 2.

The overall disposition of patients for both parts of the study on that date are summarized in the following sponsor figure for the safety population.



Abbreviations: N = the total number of subjects in the population
The Safety Population includes all subjects who were dispensed study drug. Percentages are calculated using the N values.
Note: Discontinuations that occurred during the Open-label Safety Period are included.
Note: For Part 2, "Completed" occurs when either: the subject is followed for an additional 2 years, the subject reaches 18 years of age, or the subject is followed for 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US Prescribing Information.

7.3 Demographics

Demographics for Part 2 are in the next sponsor table.

	Safety Population N = 44
Age, Part 1 (years)[a]	
N	44
Mean (SD)	11.5 (2.24)
Median	12.0
Min, Max	7, 15
Age at first dose taken in Part 2 (years)[b]	
n	44
Mean (SD)	13.1 (2.24)
Median	13.5
Min, Max	8, 17
Age group, Part 2, n (%)	
7 to 11 years	13 (29.5)
12 to 17 years	31 (70.5)
Sex, n (%)	
Male	30 (68.2)
Female	14 (31.8)
Race, n (%)	
Asian	1 (2.3)
Black / African American	12 (27.3)
White	29 (65.9)
Other	2 (4.5)
Ethnicity, n (%)	
Hispanic / Latino	3 (6.8)
Not Hispanic / Latino	41 (93.2)
Country, n (%)	
United States	31 (70.5)
Finland	0
France	0
Italy	12 (27.3)
Netherlands	1 (2.3)

Abbreviations: Max = maximum; Min = minimum; N = the total number of subjects in the population.
[a] Age in years at the first dispensation of study drug.
Note: The Safety Population consists of all subjects who were dispensed study drug. Percentages were calculated using the N value.

7.4 Adverse Events

An overall summary of all treatment-emergent adverse events that occurred during all periods of the study, as of April 30, 2018, is in the following table, which I have copied from the submission. The table is self-explanatory.

	Total N = 104
Any TEAEs	81 (77.9)
Any related TEAEs[a]	57 (54.8)
Any TEAEs leading to drug interruption	8 (7.7)
Any TEAEs leading to drug withdrawal	6 (5.8)
Any severe TEAEs	4 (3.8)
Any serious TEAEs	2 (1.9)
Any fatal TEAEs	0
Any TEAEs of special interest	37 (35.6)

Abbreviations: TEAE = treatment-emergent adverse event.
[a] Related TEAEs included events considered related or suspected to be related to study drug by the Investigator.
Note: Percentages are calculated using the N value. This table includes events with onset on or after the first dose in the study Part 1 or on or after first dose in the Part 2 of the study. Events with onset more than 30 days after the last dose of study drug in Part 1, but before first dose in Part 2, and events with onset more than 30 days after the last dose of study drug in Part 2 are excluded.

The most frequently reported treatment-emergent adverse events by preferred term were enuresis (19.2%), nausea (19.2%), vomiting (18.3%), headache (17.3%), and reduced weight (11.5%).

The total number of treatment-emergent adverse events, and the adverse event rate per 100 days of exposure are in the next sponsor table, which is applicable to all periods of the study through April 30, 2018. The table lists only those events that occurred in ≥ 5% of patients in any treatment group.

System Organ Class Preferred Term	Total N = 104 Total Events / Event Rate per 100 days
Any TEAEs	**426 / 1.044**
Gastrointestinal Disorders	94 / 0.230
Nausea	35 / 0.086
Vomiting	28 / 0.069
Diarrhoea	6 / 0.015
Constipation	6 / 0.015
Abdominal pain upper	5 / 0.012
Abdominal pain	3 / 0.007
Infections and Infestations	**67 / 0.164**
Nasopharyngitis	11 / 0.027
Upper respiratory tract infection	10 / 0.025
Gastroenteritis	6 / 0.015
Sinusitis	5 / 0.012
Pneumonia	3 / 0.007
Impetigo	3 / 0.007
Bronchitis	2 / 0.005
Eye infection	2 / 0.005
Nervous System Disorders	**51 / 0.125**
Headache	31 / 0.076
Dizziness	8 / 0.020
Renal and Urinary Disorders	**40 / 0.098**
Enuresis	35 / 0.086
Psychiatric Disorders	**38 / 0.093**
Nightmare	5 / 0.012
Somnambulism	5 / 0.012
Confusional arousal	5 / 0.012
Anxiety	2 / 0.005
Investigations	**32 / 0.078**
Weight decreased	12 / 0.029
Weight increased	5 / 0.012
Gamma-glutamyltransferase increased	2 / 0.005
Respiratory, Thoracic and Mediastinal Disorders	**19 / 0.047**
Cough	5 / 0.012
Nasal congestion	4 / 0.010
Oropharyngeal pain	2 / 0.005
Injury, Poisoning and Procedural Complications	**18 / 0.044**
Procedural pain	4 / 0.010
Contusion	3 / 0.007
Metabolism and Nutrition Disorders	**14 / 0.034**
Decreased appetite	9 / 0.022

Abbreviations: TEAE=treatment-emergent adverse event.
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in the Double-blind Treatment Period, for those subjects who received Placebo during that period. Events with onset more than 30 days after the last dose of study drug in the study are excluded.
Note: The event rate was defined as the number of events experienced divided by the number of days of Xyrem exposure as follows: 100 * Total Event Count / total Xyrem Exposure days for all subjects in the population. The Total Event count is the total number of events experienced.

A summary of treatment-emergent adverse events of special interest that occurred during all phases of the study is in the next sponsor table.

	Total N = 104
Any TEAEs of special interest	**33 (31.7)**
Psychiatric Disorders	**20 (19.2)**
Nightmare	5 (4.8)
Somnambulism	5 (4.8)
Confusional arousal	3 (2.9)
Anxiety	2 (1.9)
Acute psychosis	1 (1.0)
Affect lability	1 (1.0)
Confusional state	1 (1.0)
Depression	1 (1.0)
Irritability	1 (1.0)
Mental status changes	1 (1.0)
Mood altered	1 (1.0)
Sleep talking	1 (1.0)
Stress	1 (1.0)
Suicidal ideation	1 (1.0)
Thinking abnormal	1 (1.0)
Investigations	**12 (11.5)**
Weight decreased	12 (11.5)
Respiratory, Thoracic and Mediastinal Disorders	**4 (3.8)**
Sleep apnoea syndrome	3 (2.9)
Cheyne-Stokes respiration	1 (1.0)
Nervous System Disorders	3 (2.9)
Somnolence	2 (1.9)
Hypersomnia	1 (1.0)
General Disorders and Administration Site Conditions	**1 (1.0)**
Feeling jittery	1 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event
Note: The summary includes events experienced while receiving Xyrem, excluding events occurring in the Double-blind Treatment Period, for those subjects who received Placebo during that period.
Note: This table includes events with onset on or after the first dose in the study Part 1 or on or after first dose in the Part 2 of the study. Events with onset more than 30 days after the last dose of study drug in Part 1, but before first dose in Part 2, and events with onset more than 30 days after the last dose of study drug in Part 2 are excluded.
PTs are sorted in descending order of subject incidence.

There were no deaths or new serious adverse events reported for the period from February 10, 2017, through April 30, 2018.

During the same period from February 10, 2017, through April 30, 2018, a single additional patient who was Xyrem®-naïve withdrew from the study because of a treatment emergent adverse event: a 14-year-old boy (# (b) (6)), withdrew from Part 1 of the study (open-label safety period), on account of headache (which first developed at a Xyrem® dose of 8 g/night) and muscle pain (which first developed at a Xyrem® dose of 9 g/night); these symptoms were mild to moderate in severity and resolved when Xyrem® was discontinued.

7.5 Safety Laboratory Tests

Standard hematology, clinical chemistry, and urinalysis parameters data for this study for the period from February 10, 2017, through April 30, 2018, did not reveal any data of concern.

The analysis of growth hormone, insulin-like growth factor 1, and prolactin concentrations for the period from February 10, 2017, through April 30, 2018, revealed no data of significance; neither did the analysis of measures of precocious puberty (luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, and Tanner staging) conducted in girls < 8 years old and boys < 9 years old.

7.6 Electrocardiograms

Electrocardiographic data for Study 13-005 for the period from February 10, 2017, through April 30, 2018, were not significantly different from those provided in the original submission of this application and showed no items of concern.

7.7 Vital Signs, Height, Weight, And Body Mass Index

The additional blood pressure, pulse rate, respiratory rate, and temperature reported in this 120-day safety update did not yield any findings of significance.

No effect of Xyrem® on height was observed during the study.

Mean body weight percentile and mean body mass index percentile continued to demonstrate a slight decrease over the course of this study.

7.8 Polysomnographic Data

This 120-Day Safety Update contains cumulative polysomnographic data for the entire study.

Polysomnographic respiratory data for patients already receiving Xyrem® at study entry are in the sponsor table below. These data are based on full-night polysomnograms.

Parameters	Screening PSG (with Xyrem)[a] n = 32	End of Study PSG (with Xyrem) n = 30	Change from Screening – End of Study n = 30
	Mean (SD) Median (Q1, Q3)		
Apnea + Hypoapnea index	1.16 (1.269); 0.85 (0.25, 1.65)	2.54 (5.696); 0.50 (0.20, 1.70)	1.37 (5.331); 0.0 (-0.60, 0.70)
Apnea index	0.44 (0.750); 0.1 (0.0, 0.65)	1.63 (3.779); 0.10 (0.00, 0.50)	1.18 (3.665); 0.0 (0.00, 0.50)
Central apnea index	0.42 (0.72); 0.1 (0, 0.65)	1.53 (3.604); 0.10 (0.00, 0.40)	1.09 (3.485); 0.00 (-0.10, 0.40)
Obstructive apnea + hypoapnea index	0.73 (0.796); 0.45 (0.15, 1.05)	1.00 (3.193); 0.30 (0.00, 0.60)	0.28 (2.791); -0.10 (-0.60, 0.30)
Obstructive index	0.02 (0.072); 0 (0, 0)	0.09 (0.421); 0.00 (0.0, 0.0)	0.09 (0.420); 0.00 (0.0, 0.0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0.01 (0.071); 0 (0, 0)	0.01 (0.055); 0.0 (0.0, 0.0)	0.0 (0.093); 0.0 (0.0, 0.0)
Percent TST with SpO_2 < 90%	0.09 (0.512); 0 (0, 0)	0.10 (0.395); 0 (0, 0)	0.00 (0.676); 0 (0,0)
Total time SpO_2 is ≤ 85% during TST (minutes)	0.06 (0.336); 0 (0, 0)	0.05 (0.274); 0 (0, 0)	-0.01 (0.450); 0 (0, 0)
Total time SpO_2 is < 90% during TST (minutes)	0.46 (2.562); 0 (0, 0)	0.44 (1.668); 0 (0, 0)	-0.05 (3.199); 0 (0,0)
Mean SpO_2 during TST (%)	97.52 (0.828); 97.5 (96.95, 98.20)	96.93 (1.471); 97.00 (96.20, 98.00)	-0.58 (1.292); -0.45 (-1.20, 0.30)

Abbreviations: n = number of subjects with a value collected for the test; PSG = polysomnogram; Q1 = first quartile; Q3 = third quartile; SpO_2 = oxygen saturation; TST = total sleep time.

Polysomnographic respiratory data for patients who were Xyrem®-naïve at study entry are in the next sponsor table. These data are also based on full-night polysomnograms.

Parameters	Screening PSG (without Xyrem)[a] n = 73	End of Stable Dose PSG (with Xyrem)[a] n = 64	Change from Screening to End of Stable Dose[a] n = 63	End of Study PSG (with Xyrem) n = 58	Change from Screening – EoS n = 57	Change from End of Stable Dose – EoS n = 58
	Mean (SD); Median (Q1, Q3)					
Apnea + Hypoapnea index	1.24 (1.180); 1 (0.40, 1.70)	1.924 (4.8115); 1.1 (0.4, 1.65)	0.652 (4.9763); -0.1 (-0.8, 0.6)	1.221 (1.6102); 0.6 (0.4, 1.3)	-0.188 (1.7218); -0.3 (-1.0, 0.2)	-0.267 (1.9212); -0.1 (-0.9, 0.4)
Apnea index	0.31 (0.483); 0.10 (0.00, 0.40)	1.155 (4.6975); 0.3 (0, 0.7)	0.853 (4.7606); 0 (-0.1, 0.3)	0.460 (1.0436); 0.2 (0.0, 0.5)	0.125 (0.9869); 0.0 (-0.2, 0.3)	-0.172 (1.5568); -0.1 (0.5, 0.1)
Central apnea index	0.27 (0.452); 0.1 (0, 0.40)	1.123 (4.6531); 0.3 (0, 0.675)	0.864 (4.7214); 0 (-0.1, 0.3)	0.412 (1.0231); 0.1 (0.0, 0.4)	0.118 (0.9765); 0.0 (-0.2, 0.3)	-0.187 (1.5398); -0.1 (-0.4, 0.1)
Obstructive apnea + hypoapnea index	0.95 (0.937); 0.7 (0.30, 1.20)	0.797 (0.8989); 0.45 (0.1, 1.150)	-0.205 (0.9494); -0.2 (-0.7, 0.2)	0.8 (1.1547); 0.4 (0.1, 0.9)	-0.298 (1.2184); -0.2 (-1.0, 0.1)	-0.086 (0.9651); -0.5 (-0.6, 0.4)
Obstructive index	0.03 (0.088); 0 (0, 0)	0.03 (0.092); 0 (0, 0)	-0.01 (0.111); 0 (0, 0)	0.04 (0.229); 0.0 (0, 0)	0.01 (0.243); 0 (0, 0)	0.01 (0.197); 0 (0, 0)
Percent TST with SpO_2 < 80%	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)	0 (0); 0 (0, 0)
Percent TST with SpO_2 ≤ 85%	0 (0); 0 (0, 0)	0 (0.018); 0 (0, 0)	0 (0.018); 0 (0, 0)	0.0 (0.026); 0 (0, 0)	0.0 (0.026); 0 (0, 0)	0.0 (0.030); 0 (0, 0)
Percent TST with SpO_2 < 90%	0.00 (0.026); 0 (0, 0)	0.03 (0.167); 0 (0, 0)	0.02 (0.171); 0 (0, 0)	0.01 (0.080); 0 (0, 0)	0.01(0.087); 0 (0, 0)	0.01 (0.093); 0 (0, 0)
Total time SpO_2 is ≤ 85% during TST (minutes)	0 (0); 0 (0, 0)	0.01 (0.072); 0 (0, 0)	0.01 (0.073); 0 (0, 0)	0.02 (0.132); 0 (0, 0)	0.02 (0.133); 0 (0, 0)	0.01 (0.138); 0 (0, 0)
Total time SpO_2 is < 90% during TST (minutes)	0.03 (0.140); 0 (0, 0)	0.13 (0.826); 0 (0, 0)	0.10 (0.851); 0 (0, 0)	0.07 (0.347); 0 (0, 0)	0.03 (0.388); 0 (0, 0)	0.03 (0.395); 0 (0, 0)
Mean SpO_2 during TST (%)	97.40 (0.944); 97.3 (96.80, 98.00)	97.09 (0.998); 97.1 (96.40, 97.75)	-0.25 (0.917); -0.3 (-0.80, 0.30)	97.12 (0.951); 97.20 (96.70, 97.50)	-0.27 (1.090); -0.20 (-1.10, 0.20)	0.02 (1.083); -0.10 (-0.60, 0.50)

Abbreviations: EoS = End of study; n= number of subjects with a value collected for the test; PSG = polysomnogram; Q1 = first quartile; Q3 = third quartile; SpO_2 = oxygen saturation; TST = total sleep time.

The changes displayed above do not appear to have been clinically significant.

7.9 Columbia-Suicide Severity Rating Scale, Children's Depression Inventory, And Multidimensional Anxiety Scale For Children-10

Among subjects who took Xyrem®, two subjects responded positively to the Columbia-Suicide Severity Rating Scale. Those were the 2 subjects with serious adverse events for whom narratives have been provided earlier and are listed in the following table. A further description of those patients is not warranted.

Subject Number Age[a] / Sex / Race	Treatment Period	System Organ Class *Preferred Term*	Relationship to Study Drug	Severity Outcome
(b) (6) 13 / Male / White	Dose Titration Period	Psychiatric Disorders *Acute Psychosis*	Related	Severe Recovered / Resolved
(b) (6) 14 / Male / White	Dose Titration Period	Psychiatric Disorders *Suicidal ideation*	Related	Moderate Recovered / Resolved

[a] Age in years at the first dispensation of study drug.

A slight downward trend in mean Children's Depression Inventory T-scores in both Xyrem® naïve and Xyrem®-treated subjects was observed during the course of the study (higher scores correlate with more severe depression). Scores, however, remained within the average range.

Scores on the Multidimensional Anxiety Scale for Children-10 remained steady during the study.

8. Additional Safety Data Supporting Current Application

The sponsor has cited the following sources of data in support of the use of Xyrem® in children: postmarketing data and the published literature.

- Postmarketing data.
- Published literature.

Each of the above items is further addressed below.

8.1 Post-Marketing Data

From the launch of Xyrem® for marketing in September 2002 through October 12, 2017, the following has been the extent of exposure to Xyrem®.

(b) (4) unique pediatric patients initiated treatment with Xyrem® in the United States. These included:

- (b) (4) children < 12 years old (0 - < 12 years of age) and further consisted of 44 children less than 7 years old (0 - < 7 years of age).
- (b) (4) adolescents aged 12 to < 18 years of age.

The total cumulative exposure to Xyrem® was:

- (b) (4) patient-years for children (< 12 years of age).
- (b) (4) patient-years for adolescents ranging from 12 to < 18 years of age.

3671 instances of adverse events were reported in pediatric subjects during that subjects, included 378 instances associated with serious adverse events. Further:

- In children, adverse events reported in ≥ 5% of all instances of reports included nausea, somnolence, vomiting, headache, insomnia, and enuresis
- In adolescents, adverse events reported in ≥ 5% of all instances of reports included nausea, somnolence, vomiting, headache, dizziness, fatigue, insomnia, "condition aggravated," and decreased weight.

Serious adverse events reported in ≥ 1% of children have included seizure, sleep apnea syndrome, and vomiting.

6 deaths were reported: 4 in children and 2 in adolescents. None of the deaths seen were attributable to Xyrem® (the brief narratives provided by the sponsor are consistent with that conclusion).

Additional analyses of post-marketing data are also provided by the sponsor who has concluded that the cumulative post-marketing pediatric safety data are consistent with the post-marketing data for Xyrem® in adults and with the existing label for Xyrem® use in adults.

8.2 Published Literature

A summary review of data from 6 published studies has been presented. In those studies, 109 patients have been exposed to Xyrem® for periods ranging from 2 to 90 months.

Reasons for discontinuing study drug in those studies have included increased nightmares, suicidal ideation, dissociative feelings, lack of efficacy, unspecified adverse events, sleep loss, nausea, constipation, body ache, and dizziness.

Adverse events reported in > 10% of patients in any one study include weight loss, headache, nausea, disrupted nighttime sleep, irritability, parasomnias, dry mouth, increased awakenings, dizziness, terminal insomnia, groaning, and sleepiness.

Other safety data are also included. However, the safety data in the published literature for children using Xyrem® indicates a safety profile similar to that observed in adults.

9. Review Of Proposed Prescribing Information And Related Documents

I have reviewed the Prescribing Information proposed by the sponsor together with the sponsor proposals for a number of linked documents, namely the Medication Guide, Instructions for Use, and (modified) Risk Evaluation and Mitigation Strategy (REMS). The REMS itself is comprised of multiple documents.

That review has been assisted by the input of many other disciplines within the Agency, most of which are listed later in this review.

While I have participated in Agency deliberations regarding all the documents listed above, my own review has been primarily directed at the following sections of the Prescribing Information, proper.

Highlights of Prescribing Information.
Boxed Warning.
Section 1. Indications and Usage.
Section 2. Dosage and Administration.
Section 5. Warnings and Precautions.
Section 6. Adverse Reactions.
Section 8. Use in Special Populations.
Section 14. Clinical Studies.
Section 17. Patient Counseling Information.

As this section of my review has been complex and iterative, it is not possible to summarize here the basis for every recommendation that I have made regarding the Prescribing Information and related documents. The recommendations that I have been have been consistent with my review of the data in this application.

I am however in agreement with the finalized and agreed-upon versions of the documents listed above that are to accompany the approval letter for this application.

10. Summary Of Statistical Review

The primary statistical review of this sNDA has been performed by Dr. Xiaorong (Sharon) Yan of the Division of Biometrics I. Her review was completed on October 15, 2018.

Her review has been directed mainly at the efficacy results of the randomized, double-blind, placebo-controlled, withdrawal phase of Study 13-005, as derived from the analysis of the primary and key secondary efficacy endpoints for that study.

She has concluded that Study 13-005 has provided sufficient evidence that Xyrem® is effective as compared with placebo in treating cataplexy in patients

with narcolepsy. She has also substantiated the sponsor's main analysis of the two key secondary efficacy endpoints.

Please see the full text of Dr. Yan's review for more details.

10.1 Summary Of Interim Analysis

Dr. Yan's review has also substantiated the results of the interim analysis of the change from baseline in the weekly frequency of cataplexy attacks across the randomized, double-blind, placebo-controlled withdrawal period. As already noted (see Section 6.2), that analysis was conducted when 35 patients had completed or withdrawn early from that period of the study. The interim analysis included 18 patients on placebo and 17 patients on Xyrem®. The results of that analysis are summarized in the following table (Table 4) that I have copied from Dr. Yan's review.

Table 4 Interim Results: Change in the Weekly Number of Cataplexy Attacks

	Placebo N=18	**Xyrem N=17**
Baseline Number of Cataplexy		
Mean (SD)	12.38 (28.69)	11.79 (16.72)
Median	5.31	4.67
Min, Max	0, 125.4	0.0, 51.3
25%, 75% quartile	1.0, 10.0	0.6, 10.8
Double-blind Number of Cataplexy		
Mean (SD)	25.25 (23.86)	13.68 (21.03)
Median	21.25	5.38
Min, Max	2.5, 95.5	0, 75.1
25%, 75% quartile	14.0, 24.7	0.5, 10.0
Change in the Number of Cataplexy		
Mean (SD)	12.87 (17.43)	1.89 (8.03)
Median	12.70	0.0
Min, Max	-29.9, 56.5	-4.5, 32.1
25%, 75% quartile	3.5, 17.6	-1.0, 1.6
p-value (primary)		0.0002

Source: Reviewer's analysis

As has already been noted in this review, Amendment 4 to Study 13-005 provided for the termination of the randomized withdrawal phase of that study. Dr. Yan points out that a total of 63 patients had been randomized to that phase of the study by the time that protocol amendment had become effective at all study sites.

11. Summary Of Nonclinical Review

Dr. Melissa Banks-Muckenfuss was the primary nonclinical (pharmacology-toxicology) reviewer of this submission. Her review has primarily focused on the results of the animal toxicology study (20078509) conducted under the pediatric Written Request finalized on April 25, 2017. She has also reviewed a pilot pharmacokinetic and tolerability study of sodium oxybate in juvenile rats (Study 1301-016). Her review was completed on October 24, 2018.

The animal toxicology study conducted under the above Written Request was a 10-week study (with an 8-week recovery period) in juvenile rats of the following doses of sodium oxybate: 0, 100, 300, and 900 mg/kg orally QD).

Dr. Banks-Muckenfuss has, in summary drawn attention to the following, regarding the results of the 10-week toxicology study conducted in juvenile rats.

- Deaths were observed at doses of 300 mg/kg QD and 900 mg/kg QD, preceded by clinical signs that included uncoordinated gait, reduced activity, reduced respiratory rate, deep breathing, low carriage, partially closed eyes, and other signs; these clinical signs indicated a depressant effect of sodium oxybate on the central nervous system and on respiration. These effects were analogous to the central nervous system and respiratory depressant effects observed in humans administered Xyrem® that are described in the Prescribing Information for that drug. Other clinical signs, such as, but not limited to, reductions in food consumption, were also observed at the above doses of 300 mg/kg QD and 900 mg/kg QD in the juvenile animal study.

- Juvenile animals showed an increased sensitivity to the central nervous system and respiratory depressant effects of Xyrem®.

- The no-observed-adverse-effect level in the juvenile rat toxicity study was 100 mg/kg QD, based on the above.

- Toxicokinetic data indicated that systemic exposure to sodium oxybate increased, generally greater than dose-proportionally, with increasing doses, but also decreased with repeated dosing (i.e., in older rats). There were no sex differences in exposure to sodium oxybate. A tendency for younger rats to show higher exposures was observed in the pilot pharmacokinetic study in juvenile rats. There was considerable variability in pharmacokinetic exposure at the same dose in the juvenile rat toxicology study.

- There is no clear safety margin (based on body surface area-adjusted calculations) between the no-observed-adverse-effect level of 100 mg/kg QD in the juvenile rat toxicity study and the initial total nightly doses proposed by the sponsor for pediatric dosing (ranging from 1 gram per night to 4.5 grams per night depending on body weight). Inferences that can be drawn from safety margins that are calculated based on comparisons of pharmacokinetic data have a number of limitations that Dr. Banks-Muckenfuss has outlined in her review, but no safety margin can be delineated on that basis either.

Dr. Banks-Muckenfuss has recommended, based on the above-described lack of a safety margin, that Xyrem® **not** be approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

She does, however, note the following:

- In the juvenile rat toxicity study, dosing was initiated at an age comparable to 2 years in humans (based on the extent of central nervous system development).

On the other hand, Xyrem® is proposed for use in children aged 7 years and older.

- In pediatric subjects, Xyrem® doses are to be titrated and the total nightly dose administered in two divided doses; that was not the case in the juvenile rat toxicology study.

For further details, please see the review by Dr. Banks-Muckenfuss, who has separately concluded that the sponsor has met the terms of the pediatric Written Request finalized on April 25, 2017.

Dr. Lois Freed, supervisory pharmacologist, notes that plasma exposures at the no-adverse effect level dose (100 mg/kg) for adverse effects in juvenile rats are less than that in humans at the maximum recommended human dose of 9 g/night. She however observes that all deaths were preceded by clinical signs consistent with the known pharmacological effects of sodium oxybate and which are monitorable in humans. Dr. Freed further notes that similar adverse central nervous system effects have been observed in adults and are described in labeling. As discussed by Dr. Freed, there has been substantial use of Xyrem in pediatric patients since its approval in 2002. According to the sponsor, during this period, (b) (4) pediatric patients have received Xyrem® in the U.S., with (b) (4) below the age of 12 years and, of these, (b) (4) below the age of 7 years; no Xyrem®-related deaths have been identified. The sponsor also cited published literature, including six studies reporting safety data in children and adolescents treated with Xyrem® (see Summary of Clinical Safety in current application). In addition, this sNDA includes clinical data in the pediatric population. Dr. Freed concludes that clinical data are arguably the most relevant for determining the safety of a potential therapeutic, and that, if the clinical team concludes that the available data support approval of sodium oxybate for use in pediatric patients for the proposed indication, there is no objection to approval of the application from a nonclinical standpoint.

Additional note from this reviewer. The available clinical safety data for Xyrem®, including data derived from its use in children appear sufficient to offset the safety concerns that have arisen from the results of the juvenile rat toxicity study conducted with sodium oxybate. Thus, the available animal toxicology data do not preclude the approval of Xyrem® for use in children.

12. Summary Of Clinical Pharmacology Review

The main clinical pharmacology reviewers of this supplemental application were Drs. Kevin Krudys and Dawei Li. Their review was completed on October 23, 2018.

Drs. Krudys and Li have summarized the pharmacokinetic data in this application in their review. They have recommended that this application be approved and

have also concluded that the sponsor has met the terms of the pediatric Written Request, finalized on April 25, 2017.

Their main conclusions have been as follows.

- The pharmacokinetics of Xyrem® in children are qualitatively similar to those observed in adults.
- Plasma sodium oxybate concentrations were generally higher after the second nightly dose due to the combined effects of accumulation and food.
- Dose-proportionality assessments suggest dose proportionality in C_{max} and supra-proportionality in AUC, indicating non-linear clearance.

Drs. Krudys and Li have also made recommendations regarding the Prescribing Information proposed by the sponsor.

For further details, please see the review by Drs. Krudys and Li.

13. Summary Of Chemistry Review

The primary chemistry review of this submission was performed by Dr. Rohit Kolhatkar.

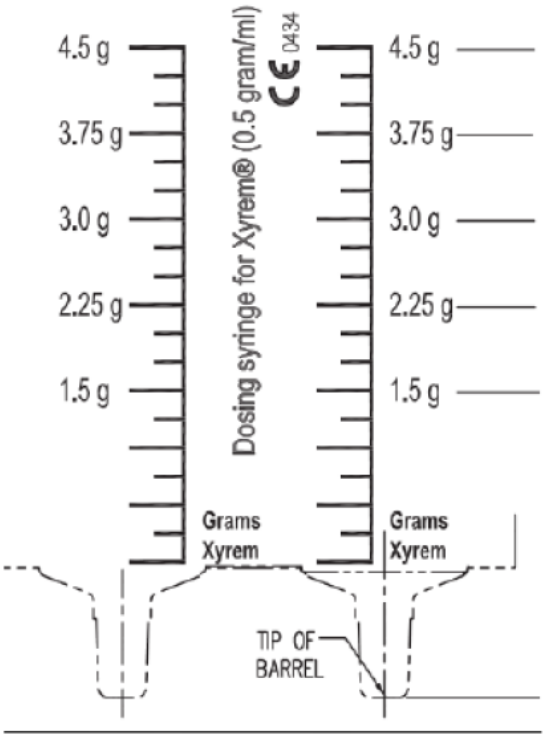
Dr. Kolhatkar has concluded that this supplemental application may be approved. He has also recommended a few changes to the Prescribing Information proposed by the sponsor.

Please see Dr. Kolhatkar's review for additional details.

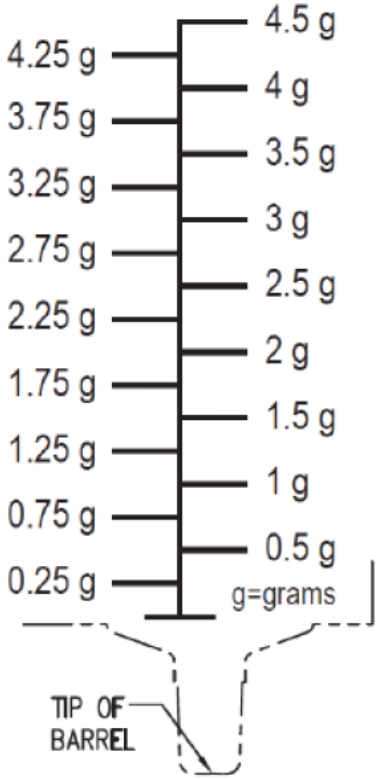
13.1 Currently-Used And Proposed Syringes

Dr. Kolhatkar's review has included a comparison of the syringe currently used for dispensing Xyrem® with the syringe proposed for pediatric use. The dispenser labels for each are in the following figure which I have copied from his review. The syringe proposed for pediatric use is intended to support the new dosing requirements in children.

Current Commercial Dispenser Label



New Label for Dispenser Covering Pediatric Doses



For details of the dispensing and dilution of individual doses of Xyrem®, please refer to the approved and proposed Prescribing Information for that drug.

14. Summary Of Office Of Surveillance And Epidemiology Reviews

Two reviews of this application have been completed by the staff of the Office of Surveillance and Epidemiology. These reviews are described further below.

14.1 Review By Division Of Risk Management (DRISK)

Dr. Yasmeen Abou-Sayed of DRISK has completed a review of the modification to the Risk Evaluation and Mitigation Strategy (REMS) proposed under this application. Her review was completed on October 16, 2018, and contains a full list of the REMS-related documents that she has reviewed.

She concluded her review by stating that the REMS modifications proposed by the sponsor in the original submission of this application, and subsequent submissions are not acceptable. At that time, a number of comments were

conveyed to the sponsor. Communications between the Agency and sponsor regarding the text of the REMS continued after the completion of her review and were continuing at the time of completion of my review.

14.2 Review By Division Of Medication Error Prevention And Analysis (DMEPA)

Dr. Ebony Whaley of DMEPA has completed a consultative review of a human factors validation study report and of labels and labeling submitted with this application; her review was completed on October 4, 2018. The human factors validation study that was conducted by the sponsor was directed at a proposed new Xyrem® dosing syringe, the container label for which has already been depicted in my summary of the Chemistry review of this submission.

Dr. Whaley has concluded that the results of the human factors validation study "*demonstrate that representative users can use the revised oral dosing syringe safely and effectively*." In her review, she has also identified text in the proposed Prescribing Information that may lead to medication errors, and has recommended changes in that text to minimize such errors.

15. Summary Of Office Of Prescription Drug Promotion (OPDP) Reviews

Two reviews have been completed by Christine Bradshaw, Regulatory Review Officer in that Office on the same date

A review completed on October 24, 2018, has responded to a consultation from this Division and the Division of Risk Management (DRISK) for a labeling review from that office regarding Prescriber Kit and Dear Healthcare Provider Letter components of the proposed modified REMS for Xyrem® associated with this sNDA. In that review, Ms. Bradshaw has acknowledged comments made by DRISK regarding the Prescriber Kit and Dear Healthcare Provider Letter components of the proposed modified REMS for Xyrem®. She states that OPDP will not be reviewing those materials as part of this supplement. She further recommends that the sponsor may submit those materials to the OPDP in compliance with advertising and promotion regulations.

A second review also completed on October 24, 2018, has responded to a consultation from this Division regarding the proposed Prescribing Information, Medication Guide, and Instructions for Use accompanying this application. That review has been combined with a review from the Office of Medical Policy Programs (by Sharon Williams, MSN) and a number of recommendations made regarding these labeling components.

An internal memorandum to the Division of Risk Management preceded the above reviews.

16. Controlled Substances Staff Review

A review of this application has been completed by Alan Trachtenberg, MD, MPH, of the Controlled Substances Staff. That review was completed on September 25, 2018

Dr. Trachtenberg has recommended that, from the perspective of the Controlled Substances Staff, this sNDA can be approved. He further notes that the proposed changes to Xyrem® labeling do not involve changes to Section 9 (Drug Abuse and Dependence) or any other sections that address drug abuse and dependence.

17. Financial Disclosure Information

Financial disclosure information has been collected only for the single clinical efficacy trial, 13-005, included in this submission.

17.1 Components Of Certification

17.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests (FDA Form 3454)

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in these studies. In regard to this list the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

17.1.2 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests (FDA Form 3455)

The sponsor has listed a single investigator, Richard K Bogan, MD, to whom such certification applied. Further, the sponsor has cited a number of reasons why that investigator that investigator was cleared for participation in Study 13-

005 and why his participation in that study was appropriate and was unlikely to have introduced significant bias into the results of the study.

17.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the single clinical study (13-005) that were submitted with this application.

18. Site Inspection Report

A Clinical Inspection Summary for this application was filed on October 16, 2018 by Roy Blay, PhD, Reviewer, Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, Office of Scientific Investigations.

Two study sites were inspected. Information for those sites and the conclusions drawn by the inspecting team are in the following table which I have copied from the Clinical Inspection Summary.

Site # Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #112 **Emmanuel Mignot, M.D., Ph.D.** Stanford Sleep Medicine Center 450 Broadway Street, M/C 5704 Redwood City, CA 94063	13-005 Subjects: 12	13-17 Aug 2018	NAI
Site #401 **Dr. Giuseppe Plazzi** Dipartimento di Scienze Biomediche e Biomotorie Ospedale Bellaria Università di Bologna Alma Mater Studiorum Via Altura 3 Bologna, Italy 40139	13-005 Subjects: 25	17-20 Sep 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

19. Fulfillment Of Terms Of Pediatric Written Request

The sponsor has fulfilled the terms of the pediatric Written Request finalized on April 25, 2017.

20. Overall Conclusion

This Supplemental New Drug Application has provided sufficient data to support the approval of Xyrem® for use in pediatric patients aged 7 years and older.

21. Recommendation

This Supplemental New Drug Application may be approved. An approval letter may accordingly be issued accompanied by product labeling that is agreed upon between the Agency and sponsor.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm
cc:
HFD-120
IND

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RANJIT B MANI
10/26/2018

ERIC P BASTINGS
10/26/2018
I concur, and will issue an approval letter for this supplement.