U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21,196
Drug Name:	Xyrem® (sodium oxybate)
Indication(s):	Nacolepsy with Cataplexy
Applicant:	Jazz Pharmaceuticals
Date(s):	Date of Submission: April 27, 2018 PDUFA Date: October 27, 2018
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan
Concurring Reviewers:	Kun Jin, Team Leader Jim Hung, Director
Medical Division:	Neurology
Clinical Team:	Ranjit Mani, Clinical Reviewer Eric Bastings, Deputy Director Billy Dunn, Director
Project Manager:	Vandna Kishore

Table of Contents

Reference ID: 4334869

LIST OF TABLES

LIST OF FIGURES

Reference ID: 4334869

1 EXECUTIVE SUMMARY

This pediatric supplemental NDA is to support the expansion of the labeling to include the pediatric use of Xyrem (sodium oxybate) oral solution for the treatment of cataplexy in patients with narcolepsy.

The Xyrem pediatric clinical program consists of a single Phase 2/3 study (Study 13-005) of Xyrem in the treatment of pediatric subjects, ages 7 to 17, with narcolepsy with cataplexy. The study was conducted under Pediatric Written Request (PWR), as amended on 25 April 2017.

Study 13-005 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem.

After reviewing the results from a pre-planned interim analysis based on 35 subjects, the Data Safety Monitoring Board (DSMB) recommended that the placebo treatment in the Double-blind Treatment Period of the trial be stopped as the prespecified stopping criterion ($p < 0.005$) was met. The interim results showed an increase of 12.7 in the median of weekly number of cataplexy attacks in patients withdrew from Xyrem and received placebo, compared to no change in patients continued in Xyrem treatment during the double-blind period with a p-value of 0.0002 in the treatment difference.

The results from the final analysis on the primary efficacy endpoint of change in weekly number of cataplexy attacks were similar to the ones from the interim analysis.

2 INTRODUCTION

2.1 Overview

Xyrem® (sodium oxybate) oral solution (NDA 21-196) is approved in the United States (US) for the treatment of cataplexy in patients with narcolepsy (2002) and for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy (2005).

Jazz Pharmaceuticals conducted one efficacy and safety study (Protocol 13-005) with Xyrem in pediatric patients with narcolepsy with cataplexy to support the application. Study 13-005 was conducted under the Pediatric Written Request.

Study 13-005 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution in pediatric subjects with narcolepsy with cataplexy.

On February 24, 2016, the Data and Safety Monitoring Board (DSMB) for this study reviewed the results from a pre-planned interim analysis of the primary efficacy based on 35 subjects

Reference ID: 4334869

having completed or discontinued from the Double-blind Treatment Period of the study. The results of this analysis showed positive efficacy on the primary endpoint, the change in the weekly number of cataplexy attacks, at a significance level of $p < 0.005$. Since this met the prespecified criterion for success, the DSMB recommended that the placebo treatment in the Double-blind Treatment Period of the trial be stopped. The DSMB further recommended that the open-label portion of the study be continued, so as not to further expose subjects to placebo treatment.

The following table presents a summary of the study.

Table 1 List of All Studies Included in This Review

	Phase and Design	**Treatment Period**	**Comparator**	**# of Subjects per Arm**	**Study Population**
13-005	Phase 3, double-blind, placebo-controlled, 2-arm, randomized withdrawal	open-label Stable Dose Period (2 weeks) and Double-Blind Withdrawal (2 weeks)	Placebo	Placebo: 32 Xyrem: 31	Pediatric patients with narcolepsy with cataplexy

Source: Reviewer's summary

2.2 Data Sources

All documents reviewed for this BLA supplement submission are in electronic form. The path to the original submission on 4/27/2018 is \\CDSESUB1\evsprod\NDA021196\0278.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified in the submission of data and study documents.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of Efficacy for Study 13-005

3.2.1.1 Study Design

The primary objectives of Study 13-005 were to evaluate the efficacy and safety of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy.

Reference ID: 4334869

The study was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution.

Children and adolescents aged 7 to 16 years diagnosed with narcolepsy with cataplexy who were being treated with Xyrem or who were Xyrem naïve, with or without concomitant stable stimulant use, were eligible to enter the study. For this study, a Xyrem-naïve subject was defined as a subject who had never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least 1 month prior to the Screening visit for reasons other than lack of efficacy and / or tolerability.

Following Screening, subjects who were Xyrem naïve entered the open-label Dose Titration Period of up to 10 weeks. Once the Xyrem dose had been optimized per the Investigator's judgment, these subjects entered the open-label Stable Dose Period with that dose. Subjects who were on Xyrem at study entry remained on their stable dose and regimen and entered the Stable Dose Period following screening. Subjects were eligible to enter the Double-blind Treatment Period if the dose and regimen of Xyrem remained unchanged during the Stable Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events due to Xyrem treatment had occurred.

Subjects entering the Double-blind Treatment Period were randomized 1:1 to receive one of the following 2 treatments during the 2-week Double-blind Treatment Period (randomized-withdrawal):

- Xyrem: Active Xyrem was continued as a double-blind treatment at the stable dose taken and regimen used in the prior 2 weeks
- Xyrem placebo: Xyrem placebo was initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

At least 100 subjects were to be enrolled in approximately 70 sites globally. It was planned to have 70 subjects entering the double-blind treatment period.

As a result of a preplanned interim analysis, which showed positive efficacy results on the primary efficacy endpoint, the protocol was amended (Amendment 4) to replace the placebo treatment in the Double-blind Treatment Period with open-label Xyrem treatment. After Amendment 4 became effective (effective date from May 17, 2016), all subjects entering the Double-blind Treatment Period received open-label Xyrem treatment. An amended Written Request was issued on April 25, 2017, reflecting this change. For administrative reasons, the term "Double-blind Treatment Period" continued to be used throughout the protocol.

A schematic description of the study design is presented in Figure 1.

Reference ID: 4334869

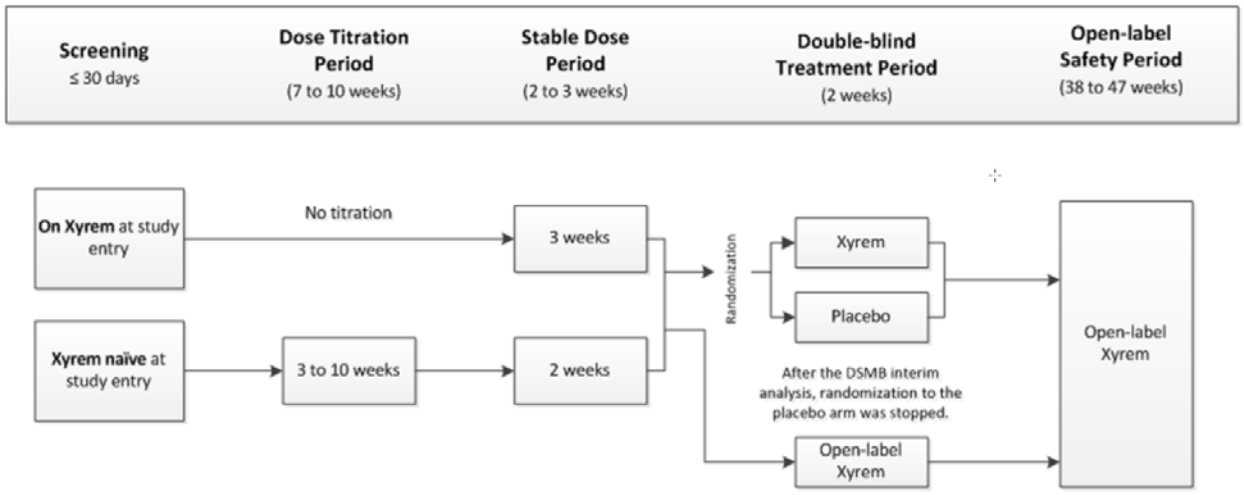

Figure 1 Study Schema
Source: Figure 1 of Clinical Study Report

3.2.1.2 Study Endpoints

The primary endpoint (Tier 1) is the change in weekly number of cataplexy attacks from the last 2 weeks of the Stable Dose Period to the 2 weeks of the Double-blind Treatment Period.

Subjects (if needed, with the help of caregiver) were to complete a cataplexy frequency diary daily in the evening to record the daily frequency of the subject's cataplexy attacks.

Key secondary endpoints (Tiers 2 and 3) are:

1. CGIc for cataplexy severity from the end of the Stable Dose Period to the end of the Double-blind Treatment Period
2. Change in the ESS (CHAD) score from the end of the Stable Dose Period to the end of Double-blind Treatment Period

3.2.1.3 Statistical Methodologies

3.2.1.3.1 General Consideration

The Efficacy Population consisted of all subjects who were randomized and who completed at least 5 days of dosing in the Double-blind Treatment Period. This population was used as the main analysis population for tables of the primary and secondary efficacy endpoints.

3.2.1.3.2 Analyses of the Primary Endpoints

Reference ID: 4334869

For the assessment of the primary efficacy endpoint, the number of weekly cataplexy attacks was determined in each period (last 14 days of the Stable Dose Period or during the Double-Blind Period) by taking the total number of cataplexy attacks reported during the period and dividing by the number of days during the period where a diary was completed. This ratio was then multiplied by 7 to determine the weekly number of attacks. Change in the weekly number of cataplexy attacks was calculated as the weekly number of cataplexy attacks during the Double-blind Treatment Period minus the weekly number of cataplexy attacks during the last 2 weeks of the Stable Dose Period (baseline).

The primary efficacy analysis compared Xyrem and Placebo using a non-parametric analysis of covariance (ANCOVA) by ranking both the baseline covariate and the change from baseline value without regard to assigned treatment group. The ANCOVA was performed with the rank for the change from baseline as the dependent variable, treatment as a factor, and the rank for the baseline value as the covariate. A sensitivity analysis was performed adjusting for age group (7 to 11 years of age and 12 to 17 years of age).

3.2.1.3.3 Analysis of Secondary Endpoints

Key Secondary Endpoints Analyses

CGIc for cataplexy severity was completed at the end of the Double-blind Treatment Period and investigators rated their impression of any change in the severity of the subject's cataplexy since baseline (defined as the end of the stable dose period) on a 7-point scale. The analysis assigned a value to each ordinal category, ranging from -3 to 3 (Very Much Worse to Very Much Improved), and the overall distribution was compared between Xyrem and Placebo by the Cochran-Mantel-Haenszel (CMH) test for row mean score difference.

An exploratory analysis compared the percent of subjects who worsened, defined as "much worse" or "very much worse", between treatments using a chi square test.

For the ESS (CHAD) endpoint, the change in score from the Stable Dose Period to the end of the Double-blind Treatment Period was compared between treatment groups using the nonparametric ANCOVA model, as described in the primary endpoint analyses. A sensitivity analysis was performed adjusting for use of stimulants in the Stable Dose Period.

3.2.1.3.4 Handling of Missing Values

For the ESS (CHAD) endpoint, a missing value in the Double-blind Treatment Period was imputed using the last available value from the Stable Dose Period (i.e., baseline value carried forward).

Reference ID: 4334869

3.2.1.3.4.1 Multiplicity Adjustment

A tiered approach was planned to control the Type 1 family-wise error rate at the two-sided 0.05 significance level. At the pre-specified interim analysis, the DSMB recommended stopping Placebo treatment during Double-blind Treatment Period due to the positive primary efficacy Results. Statistical testing of the secondary endpoints was performed after all randomized subjects completed the Double-blind Treatment Period, starting with Tier 2 in sequential order by tier (as noted in the section above, at the 0.05 significance level). If Xyrem was significantly better than Placebo, then testing continued with the next tier.

3.2.1.3.5 Interim Analysis

An interim analysis was conducted as planned after 35 subjects completed or discontinued early from the Double-blind Treatment Period. The data were reviewed by a DSMB that recommended stopping placebo treatment in the Double-blind Treatment Period and continuing the study as an open-label safety study.

Considerations for stopping the study early included the following as initially planned.

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

Stopping rules for futility and safety were also pre-specified in the protocol and assessed by the DSMB.

3.2.1.4 Study Results

3.2.1.4.1 Patient Disposition

Of the 136 subjects screened, 106 subjects were enrolled: 74 subjects were Xyrem naïve and 32 subjects were on Xyrem at study entry. Xyrem naïve subjects who entered the study underwent dose titration based on body weight category during the Dose Titration Period. About 90% of subjects achieved a tolerable and efficacious dose and entered the Stable Dose Period. Subjects on Xyrem at study entry immediately entered the Stable Dose Period. After completing the Stable Dose Period, eligible subjects entered the Double-blind Treatment Period followed by the Open-label Safety Period.

Reference ID: 4334869

Overall, as of 10 February 2017 (primary database cutoff date), a total of 17 subjects discontinued from the study during various study periods (7 subjects discontinued from the Dose Titration Period; 3 subjects discontinued from the Stable Dose Period; 1 subject discontinued from the Double-blind Treatment Period; 6 subjects discontinued from the Open-label Safety Period).

Note that the primary endpoint was met in the interim analysis, which included 35 randomized subjects. The randomization to Placebo or Xyrem during the Double-blind Treatment Period continued until Protocol Amendment 4 became effective. Therefore, additional subjects were randomized after the interim analysis and the final Efficacy population consisted of 63 subjects randomized to Xyrem (31 subjects) or Placebo (32 subjects) who completed at least 5 days of dosing in the Double-blind Treatment Period.

Subject disposition at the time of the data cut off on 10 February 2017 is depicted in Figure 2.

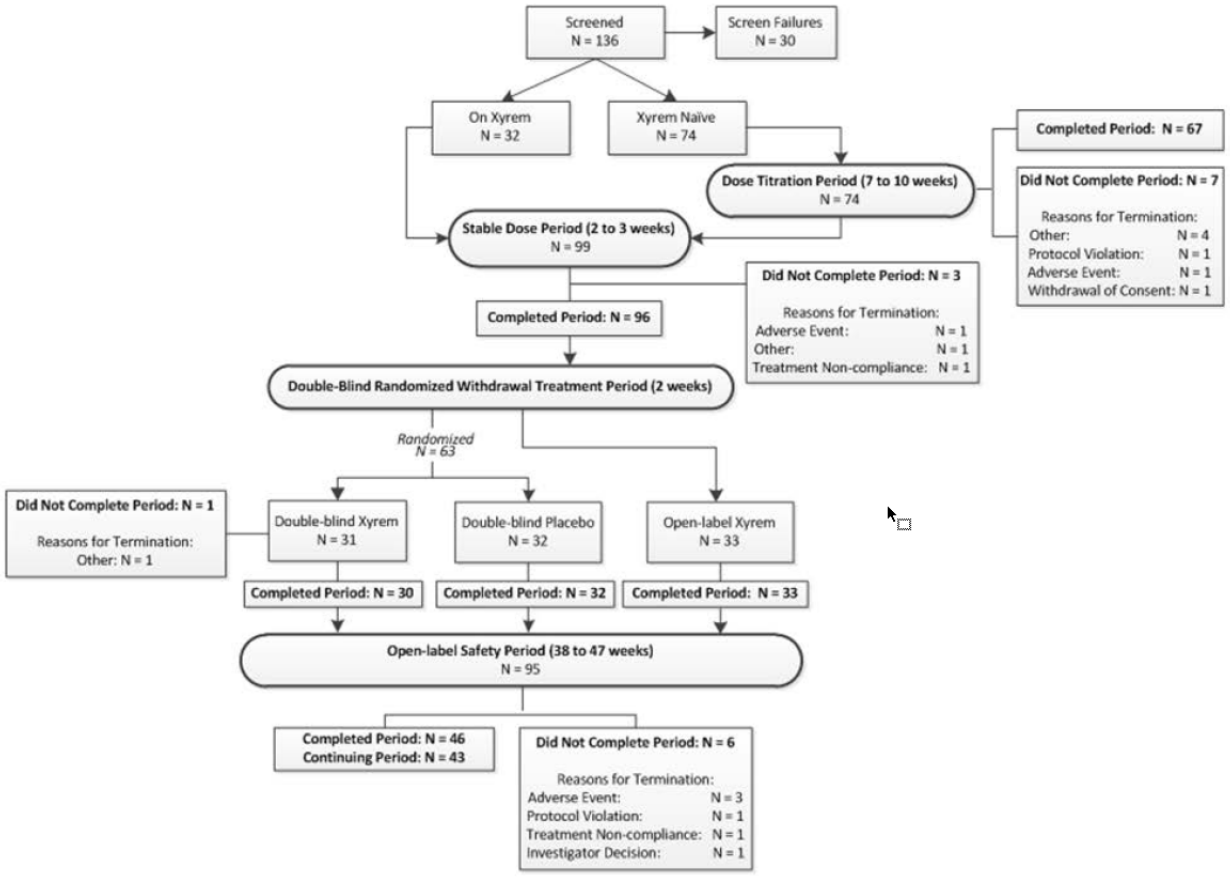

Figure 2 Patient Disposition
Source: Figure 3 of Clinical Study Report

No randomized subjects were excluded from the Efficacy population due to major deviations; therefore, the Randomized population, the Per Protocol population and the Efficacy population were equivalent.

Reference ID: 4334869

Patient Demographics

Overall, the median age was 12 years (range: 7 to 16). More subjects were enrolled in the 12 to 17-year age group (68/106 subjects, 64.2%) than in the younger 7 to 11-year age group (38/106 subjects, 35.8%). Most subjects (59.4%) were male and White (68.9%). Baseline demographic characteristics were generally balanced between treatment groups in the randomized population (Table 2).

Table 2 Demographic Characteristics (Randomized Subjects)

	Placebo N=32	**Xyrem N=31**
Age (years)		
Mean (SD)	11.8 (2.48)	11.6 (2.54)
Median	12.0	12.0
Min, Max	7, 16	7, 16
Sex, n (%)		
Male	14 (43.8)	12 (38.7)
Female	18 (56.3)	19 (61.3)
Race, n (%)		
Asian	1 (3.1)	1 (3.2)
Black / African American	7 (21.9)	4 (12.9)
White	23 (71.9)	25 (80.6)
Other	1 (3.1)	1 (3.2)
Country, n (%)		
USA	17 (53.1)	16 (51.6)
France	3 (9.4)	4 (12.9)
Italy	9 (28.1)	9 (29.0)
Netherland	3 (9.4)	2 (6.5)

Source: Reviewer's Summary and Table 8 of Clinical Study Report

3.2.1.4.2 Patient Baseline Disease Characteristics

The mean years from diagnosis for the subjects was near 2 years at the screening. About 41% of the subjects in the placebo group and 36% of subjects in the Xyrem group were on Xyrem at the entry. Most subjects (near 90%) had cataplexy severity of moderately ill to severely ill. Subjects baseline disease characteristics were generally balanced between treatment groups (Table 3).

Table 3 Baseline Disease Characteristics

	Placebo N=32	**Xyrem N=31**
Years from Diagnosis		
Mean (SD)	1.94 (1.58)	1.92 (2.17)
Median	1.63	0.99
Xyrem Status at Entry, n (%)		
Xyrem naïve	19 (59.4)	20 (64.5)
On Xyrem at Entry	13 (40.6)	11 (35.5)

Reference ID: 4334869

Cataplexy Severity, n (%)		
0=Normal, no sign of illness	0	0
1=Borderline ill	1 (3.1)	0
2=Slightly ill	1(3.1)	1 (3.2)
3=Moderately ill	5 (15.6)	5 (16.1)
4=Markedly ill	17 (53.1)	15 (48.4)
5=Severely ill	7 (21.9)	7 (22.6)
6=Most extremely ill	1 (3.1)	3 (9.7)
Mean (SD)	4.0 (0.97)	4.2 (0.95)
Baseline ESS (CHAD)		
Mean (SD)	13.9 (3.86)	13.2 (4.69)
Median	14.0	13.0

Source: Table 10 of Clinical Study Report

3.2.1.5 Efficacy Results

3.2.1.5.1 Primary Endpoint – Change in the Weekly Number of Cataplexy Attacks

The double-blind treatment period was stopped after protocol amendment 4. As a result, the interim analysis is the primary analysis for determining the efficacy.

The interim analysis included 35 subjects, 18 in the placebo group and 17 in the Xyrem group. The primary analysis of the change in the weekly number of cataplexy attacks was the analysis of covariance in ranked data.

At the baseline, the mean and median of the weekly number of cataplexy attacks were similar in the two treatment groups. During the double-blind treatment period, the weekly number of cataplexy attacks was more than doubled in the placebo group and was little changed in the Xyrem group. The mean and median change were 12.87 and 12.70, respectively, in the placebo group, compared to 1.89 and 0, respectively, in the Xyrem group. The treatment difference was statistically significant with a p-value of 0.0002, which triggered the stopping rule.

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

Reference ID: 4334869

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

Based on the positive interim results, the DSMB recommended to stop the placebo treatment. The protocol was amended (Amendment 4). The effective date of the amendment 4 varied at different sites with the earliest effective date in May 2016. A total of 63 subjects were randomized before Amendment 4 became effective.

The final efficacy data set included all 63 subjects who were randomized: 32 to the placebo group and 31 to the Xyrem group.

During the Double-blind Treatment Period, the number of weekly cataplexy attacks was more than doubled in the placebo group but was little changed in the Xyrem group - results that were similar to what were observed in the interim analysis. The median change from baseline (the last 2 weeks of the Stable Dose Period) in the weekly number of cataplexy attacks was 12.71 for subjects randomized to Placebo and 0.27 for subjects randomized to Xyrem. The comparison of the ranked change from baseline between treatments was statistically significant ($p < 0.0001$) when analyzed by ANCOVA using ranked data, adjusted by ranked baseline.

Most subjects completed 14 days of diary used for the calculation of weekly number of cataplexy attacks. The mean, median as well as the middle 50% of the number of diaries were about 14 days.

Table 5 presents a summary of the results at final analysis of the primary endpoint.

Table 5 Final Results of Weekly Number of Cataplexy Attacks

	Placebo N=32	**Xyrem N=31**
Baseline Number of Cataplexy		
Mean (SD)	16.59 (33.16)	9.60 (13.84)
Median	4.67	3.50
Min, Max	0.0, 125.4	0.0, 51.3
25%, 75% quartile	1.0, 11.0	0.6, 10.8
Double-blind Number of Cataplexy		
Mean (SD)	33.96 (46.29)	12.11 (17.36)
Median	21.25	3.77
Min, Max	0.0, 183.0	0.0, 75.0
25%, 75% quartile	6.9, 26.4	1.5, 17.7
Change in the Number of Cataplexy		
Mean (SD)	17.37 (23.89)	2.52 (7.12)
Median	12.71	0.27
Min, Max	-29.9, 103.0	-4.5, 32.1
25%, 75% quartile	3.4, 19.8	-1.0, 2.5
p-value (primary)		<0.0001

Reference ID: 4334869

Number of Diaries, days		
Mean (SD)	13.56 (1.48)	14.00 (2.03)
Median	14.0	14.0
Min, Max	10, 17	7, 18
25%, 75% quartile	13.5, 14.0	13.0, 15.0

Source: Reviewer's analysis

Sensitivity analysis by adjusting the age group yielded similar results with a p-value of <0.0001.

3.2.1.5.2 Secondary Endpoints

CGIc for Cataplexy Severity

Two subjects in the Xyrem group did not have CGIc ratings and were not included in the analysis. The analysis of the overall ratings on the 7-point scale using Cochran-Mantel-Haenszel (CMH) test (the primary test) showed a statistically significant treatment difference with a p-value of 0.0006.

At the end of the double-blind period about 66% of the subjects in the placebo group had CGIc ratings of much worse or very much worse, compared to about 17% of the subjects in the Xyrem group with the same ratings.

Table 6 CGIc for Cataplexy Severity

	Placebo N=32	**Xyrem N=31**
CGIc Ratings, n (%)		
Total Observed	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
p-value		0.0006
CGIc Worsening[1], n (%)		
Yes	21 (65.6)	5 (17.2)
No	11 (34.3)	24 (82.8)
p-value[2]		0.0001

1. Worsening = CGIc rating much worse or very much worse
2. P-value is from chi square test of proportion of patients with worsening for sensitivity analysis.

Source: Reviewer's analysis

Change in ESS (CHAD) Score

One subject in each of the treatment group did not have baseline ESS score available and were not included in the analysis. An additional subject who was randomized to placebo group did not

Reference ID: 4334869

have assessment value in the double-blind withdrawal period and had the baseline value carried forward, i.e., with 0 change. At the end of Stable-Dose period (baseline), the median ESS score was 11.0 for the placebo group and 8.0 for the Xyrem group. At the end of the double-blind treatment period, the median ESS score increased by 3 points in the placebo group and was flat in the Xyrem group. The difference in the change from baseline in the ESS core was statistically significant based on the ANCOVA with the ranked score adjusted by ranked baseline score.

Table 7 Change from Baseline in ESS (CHAD) Score at the End of Doub-blind Period

	Placebo N=31	**Xyrem N=30**
Baseline (Visit 3 – End of Stable Dose)		
Mean (SD)	10.4 (3.80	8.5 (4.35)
Median	11.0	8.0
Visit 4 (End of Double-blind)		
Mean (SD)	13.2 (4.03)	9.2 (4.81)
Median	12.0	9.0
Change from Baseline		
Mean (SD)	2.8 (3.68)	0.7 (3.22)
Median	3.0	0.0
p-value		0.0004

Source: Reviewer's analysis

Sensitivity analysis adjusting for the use of stimulants in the Stable Dose Period yielded similar results with a p-value of 0.0009.

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Ranjit Mani.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analysis of the primary endpoint by gender, race, age and geographic region were performed. Differences among the subgroups in the change of weekly number of cataplexy attacks appear to be mostly due to the difference in the baseline weekly number of cataplexy attacks. The treatment effects were consistent among the subgroup populations.

Table 8 Change in the Weekly Number of Cataplexy Attacks by Subgroup

	Placebo N=32	**Xyrem N=31**

Reference ID: 4334869

Sex		
Female		
N	15	13
Baseline Mean (Median)	25.06 (5.25)	5.85 (1.50)
Change in Mean (Median)	19.79 (16.00)	0.47 (0.00)
Male		
N	17	18
Baseline Mean (Median)	9.12 (2.69)	12.30 (7.75)
Change in Mean (Median)	15.23 (11.00)	4.00 (0.43)
Age Group		
7-11 Years		
N	14	12
Baseline Mean (Median)	19.14 (5.63)	19.39 (3.00)
Change in Mean (Median)	23.45 (18.32)	3.63 (0.13)
12-17 Years		
N	18	19
Baseline Mean (Median)	14.61 (2.80)	7.83 (4.00)
Change in Mean (Median)	12.64 (9.39)	1.81 (0.58)
Race		
White		
N	23	25
Baseline Mean (Median)	21.92 (5.38)	9.66 (4.00)
Change in Mean (Median)	20.68 (16.00)	1.92 (0.58)
Black		
N	7	4
Baseline Mean (Median)	2.00 (0.00)	2.50 (1.25)
Change in Mean (Median)	9.38 (4.21)	-1.15 (-0.44)
Region		
USA		
N	17	16
Baseline Mean (Median)	5.80 (5.38)	12.39 (6.08)
Change in Mean (Median)	13.68 (12.00)	1.97 (0.00)
Non-USA		
N	15	15
Baseline Mean (Median)	28.82 (2.92)	6.62 (3.00)
Change in Mean (Median)	21.55 (16.00)	3.10 (1.27)

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

Analysis of the change in weekly number of cataplexy attacks by Xyrem status at the study entry was performed. At the entry of the study, 13 subjects randomized to placebo and 11 subjects randomized to Xyrem were on Xyrem. Nineteen (19) subjects randomized to placebo and 20 subjects randomized to Xyrem were considered Xyrem naïve (had never been treated with ZXyrem or had discontinued Xyrem for at least one month). Treatment effect is consistent between the two subgroups.

Reference ID: 4334869

Table 9 Change in the Weekly Number of Cataplexy Attacks by Xyrem Status at Entry

	Placebo N=32	Xyrem N=31
Xyrem Status at Entry		
On Xyrem		
N	13	11
Baseline Mean (Median)	14.28 (4.50)	11.38 (3.00)
Change in Mean (Median)	13.17 (12.00)	2.43 (1.17)
Xyrem Naive		
N	19	20
Baseline Mean (Median)	18.17 (4.85)	8.62 (3.75)
Change in Mean (Median)	20.24 (13.42)	2.57 (0.13)

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No significant statistical issues were found to be deemed having significant impact on the efficacy results.

5.2 Collective Evidence

Study 13-005 has showed efficacy that is consistent at the interim and final analyses and across subgroup populations. Patients who withdrew from Xyrem had a median increase of over 12 cataplexy attacks compared to no increase in patients who continued Xyrem treatment during the double-blind treatment period. The treatment difference highly statistically significant.

5.3 Conclusions and Recommendations

Study 13-005 has provided sufficient evidence that Xyrem is effective as compared to placebo in treating cataplexy in patients with narcolepsy.

Reference ID: 4334869

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/

XIAORONG YAN
10/15/2018

KUN JIN
10/15/2018
I concur with the review.

HSIEN MING J HUNG
10/15/2018