Office of Clinical Pharmacology Review

NDA Number	21196 S30
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Submission Date	04/27/2018
Submission Type	Pediatric Efficacy Supplement
Brand Name	Xyrem
Generic Name	Sodium Oxybate oral solution
Dosage Form and Strength	Oral Solution: (b) (4) g/mL
Route of Administration	Oral
Proposed Indication	Cataplexy or excessive daytime sleepiness (EDS) in narcolepsy in patients 7 years of age and older
Applicant	Jazz Pharmaceuticals
OCP Review Team	Kevin Krudys, Ph.D., Dawei Li, Ph.D., Angela Men, Ph.D.

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1. EXECUTIVE SUMMARY

In this pediatric efficacy supplement, Jazz Pharmaceuticals is seeking approval of Xyrem® for treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older. The submission is in response to a pediatric Written Request issued on March 10, 2014 and amended on April 25, 2017.

Xyrem® is a CNS depressant currently approved for treatment of cataplexy or excessive daytime sleepiness in the adult population. In adults the recommended starting dose is 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. The dose can be increased to a total of 9 g per night.

The current submission includes the results from the pivotal pediatric clinical trial 13-005, a double-blind, placebo-controlled, randomized withdrawal study of Xyrem® in pediatric subjects with narcolepsy with cataplexy. In addition, a population PK analysis was conducted to describe the pharmacokinetics in the pediatric population and to support the proposed dosing regimen. The primary focus of this review is the evaluation of the proposed pediatric dosing regimen.

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective and we recommend approval for the proposed indications in pediatric patients 7 years of age and older. From a clinical pharmacology perspective, the applicant has met the terms of the Pediatric Written Request. The applicant should include appropriate labeling, described below, in the pediatric population.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics of sodium oxybate in the adult population are summarized in the product label. Briefly, sodium oxybate pharmacokinetics are nonlinear and are similar following single or repeat dosing of Xyrem. Following oral administration, absolute bioavailability is 88% and the average time to peak plasma concentration ranges from 0.5 to 1.25 hours. Administration of Xyrem immediately after a high-fat meal results in delayed absorption and reduction in exposure. Metabolism is the major pathway for elimination, producing carbon dioxide and water via the Krebs cycle and secondarily by beta-oxidation. Plasma levels of sodium oxybate have been demonstrated to increase more than dose-proportionally.

Pediatric PK data were collected in Study 13-005, a double-blind, placebo-controlled, randomized withdrawal, efficacy and safety study of Xyrem with an open-label PK evaluation and safety extension. Pediatric patients between the ages of 7 and 16 years who were diagnosed with narcolepsy with cataplexy, who were being treated with Xyrem or who were Xyrem naïve, were eligible to enter the

study. Dosing in subjects who were Xyrem naïve is provided in Table 1. Subjects who were on Xyrem at study entry remained on their stable dose and regimen.

Table 1: Study 13-005 Xyrem Dose Initiation and Titration

Subject Weight (kg)	Initiation Dose (Taken in 2 divided doses)[a]	Titration Regimen	Maximum Total Nightly Dose
< 30	≤ 2 g/night	≤ 1 g/night/week	6 g/night
≥ 30 to < 45	≤ 3 g/night	≤ 1 g/night/week	7.5 g/night
≥ 45	≤ 4.5 g/night	≤ 1.5 g/night/week	9 g/night

[a] At bedtime and 2.5 to 4 hours later. For children who slept more than 8 hours per night, Xyrem could be given after bedtime, while the child was in bed, in 2 equally divided doses 2.5 to 4 hours apart.

After a dose stabilization period, patients were randomized to continue double-blind treatment at the stable dose or to receive placebo at a volume and regimen equivalent to the stable Xyrem dose. Following an interim analysis, which demonstrated positive efficacy results on the primary endpoint, the protocol was amended to replace the placebo arm with open-label Xyrem treatment.

Once subjects were taking a stable dose of Xyrem, they were eligible to participate in an open-label PK evaluation. PK sampling was performed on PK Nights 1 and 2. The first nightly dose was taken at least 2 hours after a meal and the second dose was taken 4 hours after the first dose. On PK Night 1, Xyrem was administered at half the stable dose and on PK Night 2, Xyrem was administered at the full dose. Blood samples were obtained at the following times relative to the first Xyrem dose: 0, 0.75, 1.5, 2.5, 4, 4.75 and 8 hours. The PK population (N=29) consisted of 2 age groups, 7 to 11 years (N=11) and 12 to 17 years (N=18).

Noncompartmental Results

The pharmacokinetics of sodium oxybate was characterized in study 13-005. Dose proportionality assessments suggested sodium oxybate exhibited proportionality in Cmax, and supra-proportional increases in AUC, indicating nonlinear clearance. The combined effects of accumulation and food effect led to sodium oxybate plasma concentrations that were generally higher after the second nightly dose than the first nightly dose. Overall, the PK of sodium oxybate in pediatric subjects was similar to that previously observed in adults.

Analytical Section

Plasma sodium oxybate concentrations obtained in Study 13-005 were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

The lower limit of quantitation was 1.00 mcg/mL and the upper limit of quantitation was 160.00 mcg/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in Study 13-005 is provided in the table below:

	Project No.	Calibration Range (mcg/mL)	QCs (mcg/mL)	Inter-Run Precision (%CV)	Inter-Run Accuracy (%RE)
Method Validation	VJAZZ1901P1	1.00 to 160.00	1.00, 3.00, 24.00, 112.00	2.3 to 10.8	-3.4 to 1.0
Assay Performance	BJAZZ1310P1	1.00 to 160.00	3.00, 50.00, 380.00	≤4.6%	-4.7 to 1.5%

Population PK Model Results

Population PK analysis was performed with pooled pediatric and adult data. The results of the analysis are provided in greater detail in Appendix 4.1. Briefly, the final model was a two-compartment model with Michaelis-Menten elimination. The final model included a proportional food effect (meal within 2 hours) on ka, allometric scalars on Vc and Vmax (centered on a body weight of 70 kg), pediatric and child age category effects on Vc and a proportional diurnal effect (AM vs. PM dosing) on Vmax. Body weight was found to be the most significant factor on oxybate kinetics. When Xyrem is dosed as mg/kg, similar PK is predicted between adult and pediatric subjects.

2.2 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following dosing in pediatric patients 7 years of age and older:

Patient Weight	Initial Dose		Titration Regimen	Maximum Recommended Dose	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	(to clinical effect)	Take at Bedtime:	Take 2.5 to 4 Hours Later:
20 kg to <30 kg	≤ 1 g	≤ 1 g	≤1 g/night/week	≤ 3 g	≤ 3 g
30 kg to <45 kg	≤ 1.5 g	≤ 1.5 g	≤1 g/night/week	≤ 3.75 g	≤ 3.75 g
≥45 kg	≤ 2.25 g	≤ 2.25 g	≤1.5 g/night/week	≤ 4.5 g	≤ 4.5 g

3. Question Based Review

3.1 Pertinent Regulatory Background

Xyrem (sodium oxybate) was first approved for the treatment of cataplexy in patients with narcolepsy in 2002. In 2005, Xyrem was also approved for the treatment of excessive daytime sleepiness in patients with narcolepsy. Xyrem is a controlled substance and is only available through a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use. A pediatric Written Request (WR) was issued on March 10, 2014 to investigate the use of sodium oxybate oral solution in the treatment of cataplexy in narcolepsy in children and adolescents aged 7 to 17 years. The WR required PK assessment, including an analysis of dose proportionality, as part of the required efficacy and safety study. The WR was amended on April 25, 2017 in response to an interim analysis of Study 1, which concluded that there were adequate data to support the efficacy of Xyrem in the pediatric population. At that time, the Office of Clinical Pharmacology agreed to remove a requirement from the WR for an ongoing analysis of PK data to determine if a sufficient number of subjects have been enrolled to adequately characterize the PK of sodium oxybate in the pediatric population.

3.2 Clinical Pharmacology Review Questions

3.2.1 Is the proposed dosing regimen appropriate for the pediatric population for which the indication is begin sought?

(b) (4)

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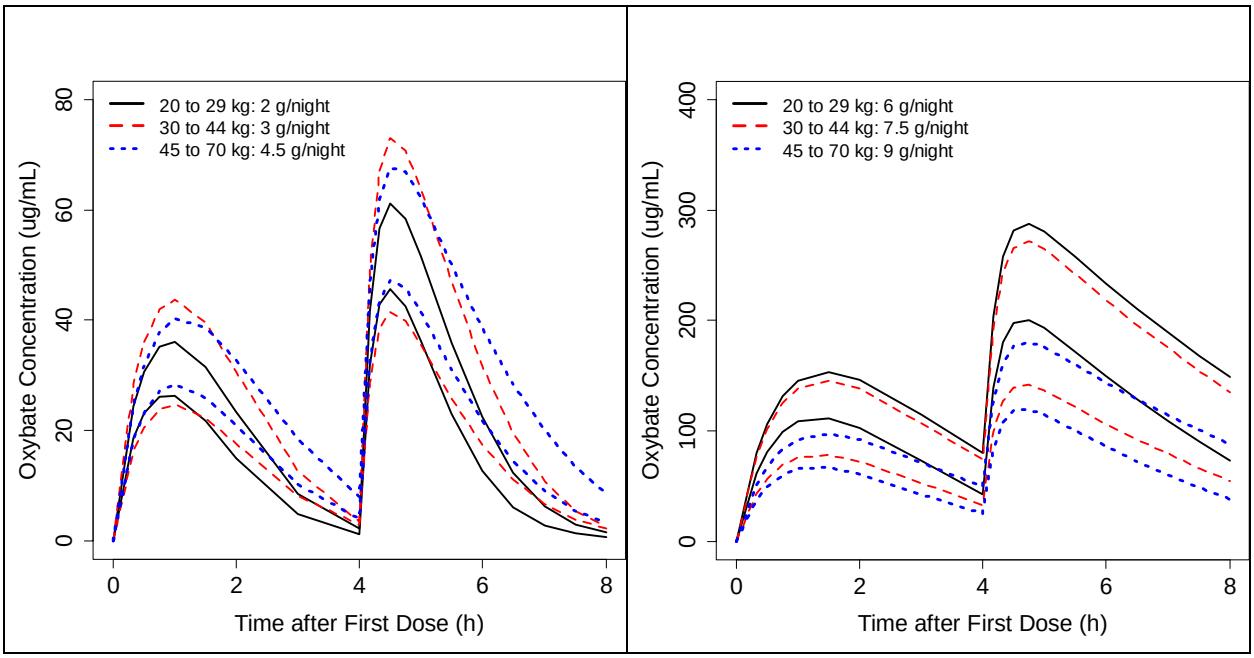
Although exposure matching is not required to establish efficacy or safety in the pediatric population, the reviewer simulated typical concentration profiles for initial and recommended total nightly doses to gain insight into potential deviations in exposure across the pediatric population. The reviewer used the applicant's final Pop PK model for simulation. Typical patients at the lower and upper ends of each weight category were simulated to provide an expected range of predicted concentrations. The results are illustrated in Figure 1 below and suggest that oxybate concentrations following the review team's dosing recommendations are largely similar across the weight categories, especially for the initial dose. Following the initial dose, the dose may be gradually titrated until an effective and tolerable dose is established.

Figure 1: Predicted Oxybate Concentration-Profiles for OCP's Recommended Dosing in Typical Patients at the Lower and Upper Ends of each Weight Category for the Initial Dose (left) and Recommended Total Nightly Dose (right)



4. APPENDICES

4.1 Population PK Analysis

The applicant performed a population PK analysis of plasma oxybate concentrations following administration of Xyrem in healthy adult subjects and pediatric and adult subjects with narcolepsy. The purpose of the analysis was to assess sources of variability and to support the proposed dosing recommendations.

Data from the following clinical studies were included in the analysis:

Table 3: Studies Included in the Population PK Analysis

Study #	Patient Population	Study Design	Doses Administered	Dosing Regimen	Blood Sample Collection
13-005	Pediatric subjects with narcolepsy with cataplexy	Double-blind, placebo controlled, randomized-withdrawal study of efficacy, safety, and PK of Xyrem	1 – 4.5 g BID	Titration of Xyrem-naïve patients to a stable nightly dose or stable nightly dose of patients already taking Xyrem (steady-state dosing)	0 (pre-dose), 0.75, 1.5, 2.5, 4 hours (pre-2nd dose), 4.75, and 8 hours following the first dose
OMC-SXB-9	Healthy adult volunteers	Open label, two period, two treatment, crossover randomized study of Xyrem PK	2 doses of 2.25 g or 2 doses of 4.5 g	2 doses of Xyrem administered 4 hours apart on Study Days 1 and 8	Pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.17 4.33, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9 and 10 hours after the first dose
09-002 (Treatment A Only)	Healthy adult volunteers	Open label, randomized, relative bioavailability crossover study of Xyrem sustained-release tablet versus Xyrem oral solution	Treatment A: 2 doses of 3 g	Administration of 2 doses of Xyrem 4 hours apart	Treatment A: pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, and 12 hours after administration of the first 3 g dose of solution
OMC-SXB-10	Narcoleptic adult subjects	Open label, two period study to compare single dose versus 8-week dosing of Xyrem	4.5 g Xyrem qhs for 8 weeks	Single and steady-state administration of Xyrem	Pre-dose and 0.17 (10 minutes), 0.33 (20 min), 0.5 (30 minutes), 0.75 (45 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, and 7 hours after administration of each of the two 4.5 g test dose of solution.
13-010	Healthy adult volunteers	Open label, randomized crossover study of PK, bioavailability, bioequivalence, and food effect of Xyrem	Treatment C: 4.5 g Xyrem oral solution fasted Treatment D: 4.5 g Xyrem oral solution fed Treatment G: 4.5 g Xyrem oral solution fasted	Administration of 2 doses of Xyrem 4 hours apart	Pre-dose and at 0.17 (10 minutes), 0.33 (20 min), 0.5 (30 minutes), 0.75 (45 min), 1 (60 min), 1.25 (75 min) 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours after administration of a single 4.5 g Xyrem dose

Source: Population Pharmacokinetics Report, Appendix 1, Page 49

The PK dataset included PK samples from 174 subjects, including 29 (16.7%) pediatric subjects and 145 (83.3%) adult subjects. There were a total of 3775 observations, including 333 (8.8%) from pediatric

subjects and 3442 (91.2%) from adult subjects. The median age of the pediatric subjects was 12 years (range: 8 to 16 years) and the median body weight was 60.8 kg (range: 31 to 129 kg). One subject (b) (6)) from Study 13-005 was removed from the analysis because the subject had a quantifiable pre-dose concentration and had a PK profile inconsistent with the expected PK of oxybate.

Population PK Model

Structural model: Two-compartment model with first-order absorption and Michaelis-Menten clearance. PK parameters include Vmax, Km, Vc, Vp, ka, k23 and k32

Interindividual variability: Proportional. The data supported variability on Vmax, Km (block), Vc and ka

Residual Variability: Proportional error model

Interoccasion variability: included on Vmax and Km

Covariates: A forward ($p<0.05$) and backward ($p<0.001$) elimination process was used to evaluate covariate effects. Measures of body size, age, sex, race, disease status, prandial status, diurnal factors and bioanalytical methods were assessed. The potential relationship was characterized using linear, power or dichotomous models, depending on the covariate. The final model included a proportional food effect (meal within 2 hours) on ka, allometric scalars on Vc and Vmax (centered on a body weight of 70 kg), pediatric and child age category effects on Vc and a proportional diurnal effect (AM vs. PM dosing) on Vmax

Final parameter estimates are shown in Table 4.

Table 4: PK Parameter Estimates for the Final Pop PK Model

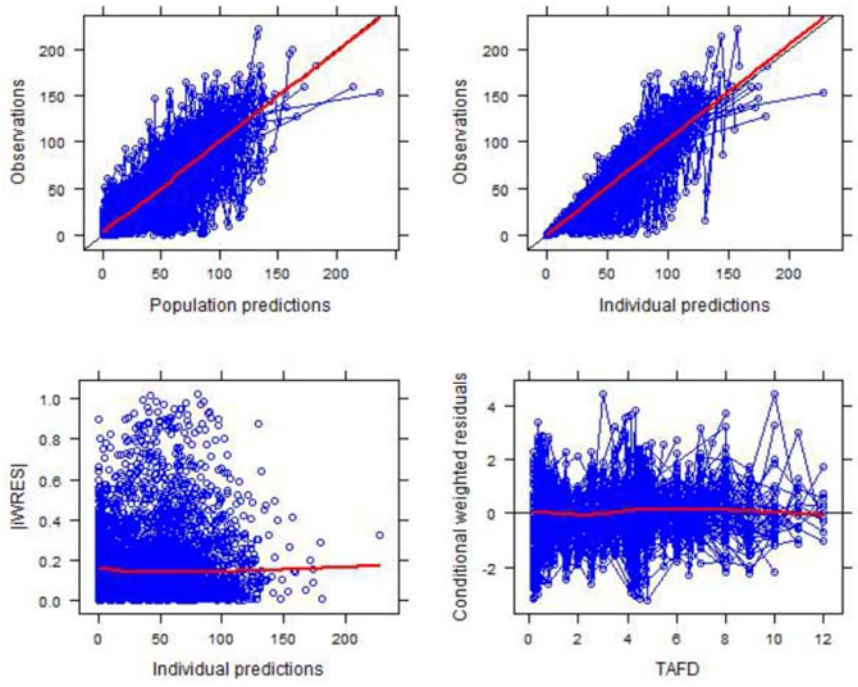
	NONMEM			Bootstrap	
Parameter (units)	**Estimate**	**IIV**	**IOV**	**Median**	**2.5th to 97.5th Percentile**
Vmax (mg/h)	1508	37.7%	10.2%	1503	(1357, 1699)
Km (mg/L)	22.0	41.4%	24.5%	22.0	(17.74, 26.78)
Central Compartment Volume of Distribution (VC) (L)	29.5	11.8%	NA	29.4	(28.35, 30.51)
Peripheral Volume of Distribution (VP) (L)	5.33	NA	NA	5.31	NA
Ka (1/hr)	4.12	47.2%	NA	4.08	(3.57, 4.76)
F (NA)	1.00 (Fixed)	NA	NA	1	Fixed
K23 (1/hr)	0.0968	NA	NA	0.0969	(0.0655, 0.1407)
K32 (1/hr)	0.536	NA	NA	0.536	(0.449, 0.633)
Food Effect on Ka (NA)	-0.681	NA	NA	-0.682	(-0.741, -0.61)
AS Exponent on VC (NA)	0.650	NA	NA	0.649	(0.506, 0.812)
AS Exponent on Vmax (NA)	0.633	NA	NA	0.619	(0.434, 0.801)
Diurnal Effect on Vmax (NA)	-0.177	NA	NA	-0.177	(-0.2438, -0.1106)
Pediatric Age Category on VC	0.201	NA	NA	0.193	(0.0897, 0.3213)
Child Age Category on VC	-0.328	NA	NA	-0.318	(-0.518, -0.124)
Proportional Error (%CV)	28.1	NA	NA	28.1	(26.6, 29.5)

NOTE: Child age category = 7-11 years; pediatric age category = <18 years; Peripheral volume of distribution calculated as (K23/K32)*VCNA=Not available; AS = Allometric scaling

Source: Population Pharmacokinetics Report, Table 3-2, Page 30.

Basic goodness-of-fit plots and visual predictive checks are illustrated in Figure 2 and Figure 3, respectively.

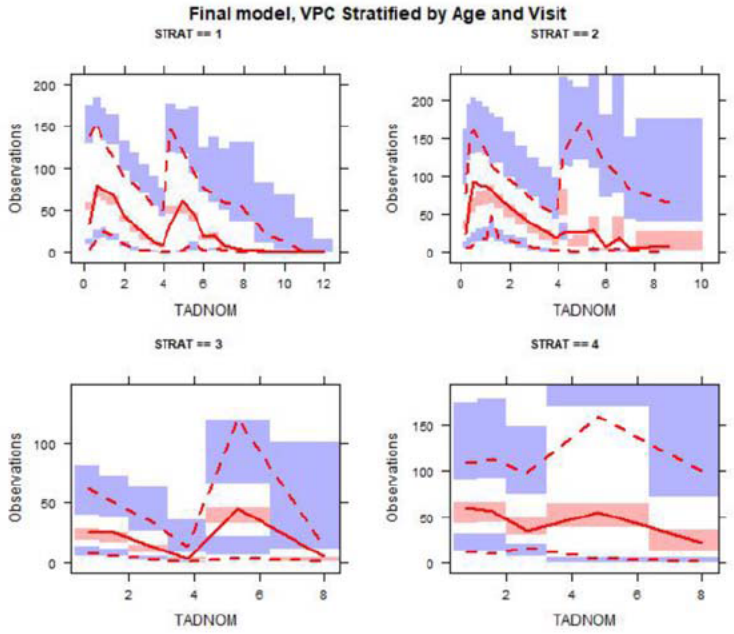
Figure 2: Basic Goodness-of-Fit Plots for Final Model



Upper Left plot is Predicted (PRED) vs Observed (DV), upper right is Individual Predicted (IPRED) vs DV, lower left plot is Individual Weighted Residuals (IWRES) vs IPRED, and lower right plot is Conditional Weighted Residuals (CWRES) vs Time After First Dose (hours) for the Final Pharmacokinetic Model of Oxybate

Source: Population Pharmacokinetics Report, Figure 3-2, Page 27.

Figure 3: Visual Predictive Check for Final PK Model



TADNOM (x axis) is nominal time after dose; y axis is concentration (µg/mL). The upper left plot (Stratum [STRT] 1) is adult population visit 1, the upper right plot (Stratum 2) is adult population visit 2, the lower left (Stratum 3) is pediatric population visit 1, and the lower right plot (Stratum 4) is pediatric population visit 2. The solid red line is the median of the observed data vs time after nominal dose time (TADNOM), the dashed red line is the upper and lower 95% range for the observed data. The red shaded are is the 95% prediction interval (PI) for the median, based on the simulations, and the blue shaded areas are the 95% PI for the upper and lower 95% range of the simulated data. Visit 1 is PK night 1 in Study 13-005 and the first period for the remaining studies. Visit 2 is PK night 2 in Study 13-005 and the second period for the remaining studies.

Source: Population Pharmacokinetics Report, Figure 305, Page 31.

The applicant concludes that body weight is the most significant factor on oxybate kinetics and that when Xyrem is dosed as mg/kg, similar PK is predicted between adult and pediatric subjects. Simulations were performed for different mg/kg doses, but not for the proposed doses.

Reviewer's Comments: The structure of the applicant's final Pop PK model is generally aligned with previous knowledge of oxybate pharmacokinetics. The Michaelis-Menten parameterization is reasonable as pharmacokinetics are known to be nonlinear and show greater than dose proportionality. According to the label, administration of Xyrem after a high-fat meal resulted in delayed absorption and reduction in exposure. The diurnal covariate estimated in the model is not relevant for the pediatric data because all data was collected at night in this population. The categorical age-based covariate on Vc does not appear to be supported by a mechanistic basis, although the reviewer agrees with the applicant that this covariate is not clinically significant. Based on parameter estimates and goodness-of-fit plots, it appears that the model provides an adequate description of the time course of oxybate concentrations.

(b) (4)

4.2 Individual Study Review

Study 13-005: A Double-blind, Placebo-Controlled, Randomized-Withdrawal, Multi-center Study of the Efficacy and Safety of Xyrem with an Open-label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy.

Objectives:

The primary objectives of this study are:

- Evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy.
- Evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to 1 year.

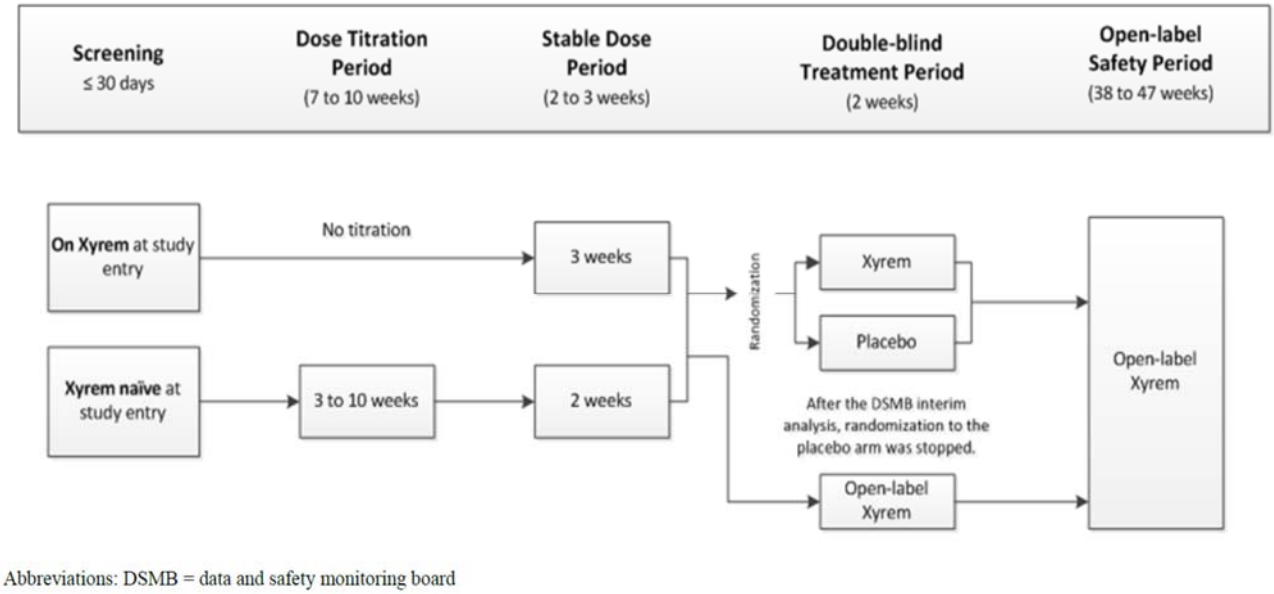
The secondary objectives of this study are:

- Evaluate the efficacy of Xyrem in the treatment of EDS in pediatric subjects with narcolepsy with cataplexy.
- Characterize the PK of Xyrem in pediatric subjects (ages 7 to 17 years) with narcolepsy with cataplexy.
- Evaluate the safety of titrating Xyrem in pediatric subjects to an effective and tolerable dose.

Study Design:

This study was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution (See Figure 4). Pediatric subjects between the ages of 7 and 17 who were diagnosed with narcolepsy with cataplexy, who were being treated with Xyrem or who were Xyrem naïve, were eligible to enter the study.

Figure 4. Study Schema



Abbreviations: DSMB = data and safety monitoring board

Study Population:

100 subjects planned, 63 subjects randomized in the Efficacy population, 106 subjects in the Safety population.

Key Inclusion Criteria:

- Male or female subjects aged 7 to 16 years at study entry
- Had a primary diagnosis of narcolepsy with cataplexy
- Was positive for the Human Leukocyte Antigen (HLA) DQB1:0602 haplotype
- Had a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment

Key Exclusion Criteria:

- Narcolepsy secondary to another medical condition, e.g., CNS injury or lesion
- Succinic semi-aldehyde dehydrogenase deficiency (SSADH)
- Evidence of sleep-disordered breathing
- Oxygen saturation level < 95% for at least 5 minutes on room air, or subjects with known or suspected respiratory difficulty, or any condition that could have compromised a subject's breathing
- Positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study

Study Treatment:

For subjects who were Xyrem naïve, Xyrem therapy was initiated based on the subjects' weight as shown in the table below. Xyrem doses were administered in two equally divided doses. Subjects were titrated on Xyrem to achieve maximum clinical benefit in cataplexy and EDS while maintaining tolerability. Dose adjustment during the open-label Dose Titration Period occurred based on the subject's weight to a dose level targeted to be no higher than the maximum dose described in the Table below in up to 10 weeks.

The study drug titration rate was ≤ 1 g/night/week for subjects < 45 kg, and ≤ 1.5 g/night/week for subjects ≥ 45 kg. The dose could have been incrementally titrated more frequently than weekly, as long as the total weekly increase was no more than 1 g/night/week in subjects < 45 kg and no more than 1.5 g/week in subjects >45 kg. All injections were administered in the same thigh but at different locations.

Table 5. Xyrem Dose Initiation and Titration for Xyrem Naïve Subjects

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

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

Pharmacokinetics:

Pharmacokinetic parameters were derived from individual plasma sodium oxybate concentration-time data over 4 hours following the first nightly dose. The PK parameters for plasma sodium oxybate concentrations included: the area under the plasma concentration time curve (AUC), AUC0-4 and AUC0-infinity, maximum plasma drug concentration (Cmax), half-life (t1/2), and time to maximum plasma drug concentration (Tmax), over the first 4-hour dosing interval. In addition, sodium oxybate concentrations at 4.75 hours (0.75 hours after the 2nd dose) and 8 hours (4 hours after 2nd dose) were measured to estimate peak and residual exposure associated with the second nighttime dose. Dose proportionality was based on the ratio between PK Night 2 (full stable dose) vs PK Night 1 (half of the stable dose) for AUC0-4 and Cmax values.

Bioanalytical Methods:

A liquid chromatography tandem mass spectrometry (LC-MS/MS) method was validated for the determination of sodium oxybate in human plasma for the analysis of pharmacokinetic samples for Study 13-005. Summary of the validated analytical methods and bioanalytical assay performance for Sodium Oxybate are presented in the Table 6.

Table 6. Summary of the Validated Analytical Methods for Sodium Oxybate

	Analyte	Sensitivity (LLOQ) (mcg/mL)	Calibration Range (mcg/mL)	QCs (mcg/mL)	Inter-Run Precision (%CV)	Inter-Run Accuracy (%RE)
Method Validation	Sodium Oxybate	1.00	1.00-160	LLOQ, 3.00, 24.0, and 112	2.3 to 10.8	-3.4 to 1.0
Assay performance	Sodium Oxybate	1.00	1.00-160	3.00, 24.0, and 112	≤4.6%	-4.7 to 1.5%

Safety Evaluations:

Safety was assessed by the incidence of TEAEs, and descriptively for vital signs, 12-lead ECG, PSG parameters, clinical laboratory results, assessments of growth and precocious puberty, and the C-SSRS, CDI 2: SR[S], and MASC-10 assessments.

Statistical Methods:

Pharmacokinetics were assessed and summarized by age group (7 to 11 and 12 to 17 years old) and overall.

Sodium Oxybate Concentration

For each PK Night, sodium oxybate concentrations were summarized by sampling time point: predose (0), 0.75, 1.5, 2.5, 4 (before the second dose), 4.75, and 8 hours following the first dose. Assessments at 4.75 and 8 hours represent the peak concentration and C4h after the second dose. All sodium oxybate concentrations recorded below the limit of quantification (BLQ) were imputed with a concentration of 0.

Descriptive summary statistics along with the coefficient of variation (CV%) were presented for each age group and overall for each Xyrem dose by time point.

PK Parameters

PK parameters such as Tmax, Cmax, AUC0-4, AUC0-infinity and half-life (t1/2) were derived based on individual plasma sodium oxybate concentration-time data following the first dose. Descriptive summary statistics along with CV%, geometric mean, and geometric standard deviation were presented for each age groups and overall for each Xyrem dose.

Dose Proportionality

For subjects in the PK Completer population, analyses for dose proportionality were performed for AUC0-4 and Cmax. The analyses were based on the ratio between PK Night 2 vs PK Night 1 for AUC0-4 and Cmax values. For each parameter, the natural log transformed value on PK Night 2 minus the natural log transformed value on PK Night 1 was the response variable. The estimated mean difference and 90% confidence interval were back-transformed to ratio scale by exponentiation in order to interpret the results in ratio scale. If a value of 2 was contained within the 90% confidence interval, it indicated proportionality.

RESULTS

Pharmacokinetics:

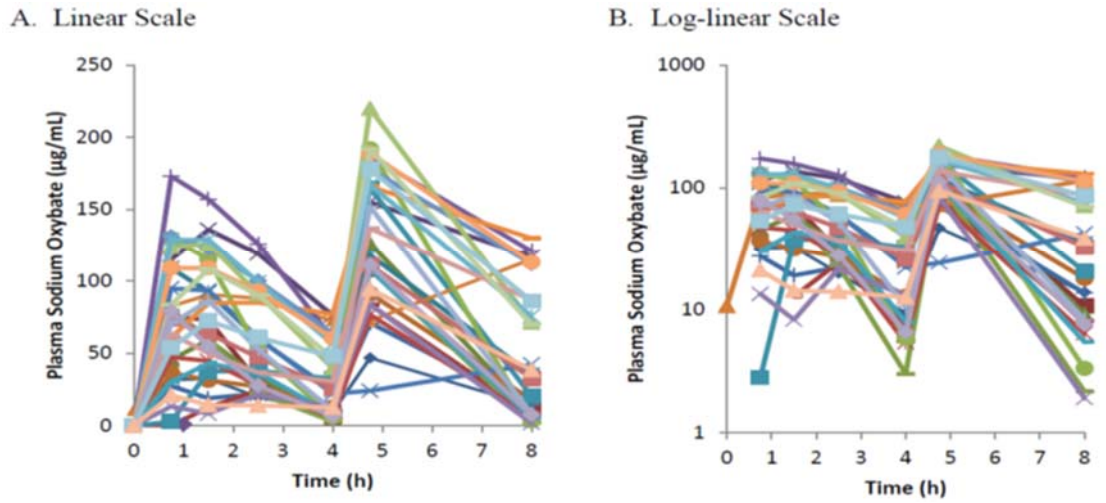
Pharmacokinetic results were obtained for the PK Completer population (N = 29), which comprised the two age groups, 7 to 11 years (N = 11; 37.9%) and 12 to 17 years (N = 18; 62.1%). There were no apparent differences in Xyrem PK characteristics between the 2 age groups.

PK sampling was performed on PK Nights 1 and 2, both of which occurred while subjects were receiving a stable dose of Xyrem. On PK Night 1, Xyrem was administered at approximately half of the stable dose, and on PK Night 2 Xyrem was administered at the full stable dose. Data from PK Night 1 (half of stable dose) informed dose proportionality, while data from PK Night 2 (full stable dose) informed exposure to drug at the stable dose. As exposure at the full stable dose is more relevant to safety and efficacy, the summary of PK results focuses mainly on the results from PK Night 2.

Sodium Oxybate Plasma Concentration-Time Profiles

Sodium oxybate plasma concentration-time profiles following administration of Xyrem at the full stable dose are shown in Figure 5. The plasma concentration-time profile presented on a log-linear scale (Figure 5, panel B) shows large variation in the terminal slopes.

Figure 5. Plasma Sodium Oxybate Concentration-time Profiles (Individual subject)



Xyrem Pharmacokinetic Parameters

For the first nightly dose on PK Night 2, the median Tmax ranged from 0.75 to 2.5 hours, and the mean Cmax and AUC0-4h values ranged from 24.3 to 92.7 µg/mL and 52.0 to 273 µg•mL/h, respectively (Table 7).

Table 7: Sodium Oxybate PK Parameters for the First Nightly Dose of Xyrem (PK Night 2, PK Population)

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.

There was no apparent association between the magnitude of the gram dose of Xyrem and either Cmax and AUC0-4h. The absence of a relationship was most likely attributable to the wide range of body weights in the PK population, which resulted in a large variation in the mg/kg doses.

Dose Proportionality

Dose proportionality assessments were based on within-subject comparisons of the 2 PK Nights, where Cmax and AUC0-4h values were expressed as ratios between PK Night 2 (full stable dose) and PK Night 1 (half of the stable dose). As PK Night 2 used a 2-fold higher dose, a mean ratio of 2.00 would suggest dose proportionality. For Cmax, the mean ratio was 1.97 and the 90% CI was 1.67 to 2.31. As the 90% CI included 2.00, the assessment suggested that Cmax was dose proportional. For AUC0-4h, the mean ratio was 2.53 and the 90% CI was 2.18 to 2.94. As the lower bound of the 90% CI was greater than 2.00, AUC0-4h was concluded to be supra-proportional.

Comparison with Historic PK Results in Adults

In both the pediatric and adult populations, the PK is nonlinear (concentration-dependent), plasma exposure increases supra-proportionally with dose, and plasma concentrations are higher with the secondly nightly dose than after the first owing largely to the effect of food on the rate of absorption. However, the PK results for pediatric subjects in Study 13-005 were generally more variable as compared to PK results for Xyrem in adults. This is due to differences in study design for adult and pediatric PK investigations, as well as the extent of variation in body weights, both of which affected the extent of variation in dose range.

Safety:

Safety assessments conducted during Study 13-005 demonstrated Xyrem was tolerated by pediatric subjects with narcolepsy. The types of TEAEs that occurred in this study were similar to previous reports in studies of narcolepsy in adults. No new safety concerns with regard to death, SAEs, or other significant AEs were identified.

CONCLUSIONS:

The PK of Xyrem in pediatric subjects was qualitatively similar to that observed in adults. The combined effects of accumulation and food effect led to sodium oxybate plasma concentrations that were generally higher after the second nightly dose than the first nightly dose. Dose proportionality assessments suggest Xyrem exhibited proportionality in Cmax, and supra-proportional increases in AUC, indicating nonlinear clearance.

Study 13-002: A Randomized Crossover Study to Evaluate the Bioavailability and Bioequivalence of Xyrem® versus Xyrem® Prepared with a Flavored Diluent Solution in Healthy Subjects

Objectives:

The primary objective of this study was to evaluate the pharmacokinetics (PK) of Xyrem prepared with a flavored diluent solution and to assess its relative bioavailability and bioequivalence compared with Xyrem prepared with water.

The secondary objective of this study was to assess the relative safety and tolerability of Xyrem prepared with a flavored diluent solution compared with Xyrem prepared with water.

Study Design:

This was a Phase 1, two-period, open-label, randomized, single-dose crossover study. Following screening and baseline procedures, on Day 1 eligible subjects were randomized 1:1 to treatment sequence AB or BA:

- Treatment A – 4.5 g dose of Xyrem prepared with 60 mL flavored diluent administered orally as a single dose
- Treatment B – 4.5 g dose of Xyrem prepared with 60 mL water (per product label) administered orally as a single dose

Subjects received the first treatment on Day 1 and the second treatment on Day 3 (1-day washout). For both treatments, subjects received study drug in the morning following a 10-hour fast and continued fasting for an additional 4 hours after dosing. After swallowing Treatment A or Treatment B, subjects were required to drink 180 mL of water.

Number of Subjects:

A total of 34 subjects were enrolled, received at least one study treatment (safety population), and provided evaluable PK data for at least one treatment regimen (PK population). A total of 32 subjects completed both of the two treatment periods and provided evaluable PK data for both treatment regimens (PK completer population). Of these 32 subjects, 24 did not vomit within 2 times the median Tmax in either treatment and were included in the statistical analysis of variance (ANOVA).

Pharmacokinetics:

Sodium oxybate PK profiles following single doses of Treatments A and B were characterized over an 8-hour period, based on blood samples (4 mL each) collected predose and at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours postdose following administration of each treatment. The plasma PK parameters for sodium oxybate included area under the plasma concentration-time curve (from Time 0 to Time t of the last quantifiable concentration [AUC0-t], and from Time 0 to infinity [AUC0-inf]), maximum plasma concentration of sodium oxybate (Cmax), time to maximum plasma concentration (Tmax), apparent elimination rate constant (Kel or λz), and half-life (t1/2).

Bioanalytical Methods:

A liquid chromatography tandem mass spectrometry (LC-MS/MS) method was validated for the determination of oxybate in human plasma in human plasma for the analysis of pharmacokinetic samples for Study 13-002. Summary of the validated analytical methods and bioanalytical assay performance for oxybate are presented in the Table 8. The final oxybate data were multiplied by the conversion factor of 1.211 (=molecular weight of sodium oxybate/molecular weight of γ-hydroxy butyric acid =126.09/104.10) for their equivalent sodium oxybate concentrations.

Table 8. Summary of the Validated Analytical Methods and Assay Performance for oxybate

	Analyte	Sensitivity (LLOQ) (mcg/mL)	Calibration Range (mcg/mL)	QCs (mcg/mL)	Inter-Run Precision (%CV)	Inter-Run Accuracy (%RE)
Method Validation	Oxybate	0.75	0.75 to 192	LLOQ, 2.25, 36, and 144	2.9 to 11.5	-0.9 to 8.5
Assay performance	Oxybate	0.75	0.75 to 192	2.25, 36, and 144	≤3.5%	-0.9 to 1.3%

Safety Evaluations:

Safety was evaluated by AEs, clinical laboratory (chemistry, hematology, coagulation, and urinalysis), vital signs, Oxygen saturation by pulse oximetry, Physical examination, 12-lead electrocardiogram (ECG).

Statistical Methods:

Sodium oxybate plasma concentrations and PK parameters were summarized by treatment regimen using descriptive statistics. PK concentration-time profiles were plotted by treatment and by subject. ANOVA models of loge transformed parameter values for the AUC0-t, AUC0-inf, and Cmax parameters for the PK completer population were provided to compare Xyrem prepared with flavored diluent (test) and Xyrem prepared with water (reference). The models included terms for sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The relative bioavailability of the flavored treatment was determined as the ratio and 90% confidence interval (CI) of AUC0-t, AUC0-inf, and Cmax values compared with the unflavored treatment. The assessment of bioequivalence was based on the bioequivalence criterion (90% CIs of the ratios falling within 80% to 125%) defined by the FDA

Results:

Pharmacokinetics:

Following the administration of single doses of Xyrem prepared with flavored diluent (Treatment A) or Xyrem prepared with water (Treatment B), mean concentration-time profiles were generally similar for both treatments. The mean sodium oxybate Cmax value was 154 µg/mL for both Treatments A and B. Mean AUC0-inf values were 325 and 312 µg·h/mL, mean t1/2 values were 0.60 h and 0.61 h, and median Tmax values were 0.75 h and 0.50 h, for Treatments A and B, respectively (see Table 9 below).

Table 9. Sodium Oxybate Plasma Pharmacokinetic Parameters Following a Single Dose of Sodium Oxybate Prepared with Flavored Diluent or with Water (PK Population)

Parameter (units)		Treatments	
		A Xyrem prepared with flavored diluent	B Xyrem prepared with water
C_{max} (µg/mL)	N	24[a,b]	25[a]
	Mean	154	154
	SD	41.4	29.6
	CV%	26.9	19.3
	Min, Max	86.0, 269	95.5, 208
	Geometric Mean	149	151
	Geometric SD	1.29	1.22
T_{max} (h)	N	24[a,b]	25[a]
	Median	0.75	0.50
	Min, Max	0.25, 2.00	0.50, 2.03
Kel (λ_z) (h^{-1})	N	24[a,b]	25[a]
	Mean	1.22	1.19
	SD	0.311	0.306
	Min, Max	0.781, 2.03	0.806, 2.16
$t_{1/2}$ (h)	N	24[a,b]	25[a]
	Mean	0.60	0.61
	SD	0.14	0.14
	Min, Max	0.34, 0.89	0.32, 0.86
AUC_{0-t} (µg·h/mL)	N	24[a,b]	25[a]
	Mean	324	311
	SD	110	97.9
	CV%	34.1	31.5
	Min, Max	151, 682	180, 559
	Geometric Mean	307	297
	Geometric SD	1.39	1.35
AUC_{0-inf} (µg·h/mL)	N	24[a,b]	25[a]
	Mean	325	312
	SD	111	98.3
	CV%	34.0	31.5
	Min, Max	152, 684	182, 562
	Geometric Mean	309	299
	Geometric SD	1.39	1.35

Treatment A: 4.5 g dose of Xyrem prepared with 60 mL flavored diluent administered orally as a single dose
Treatment B: 4.5 g dose of Xyrem prepared with 60 mL water administered orally as a single dose
Note: Geometric mean is calculated as the antilog of the arithmetic mean of the natural log-transformed values.
[a] Subjects (b) (6) were excluded due to vomiting within 2 times the median T_{max}.
[b] Subject 001-0012 discontinued the study early and did not receive Treatment A.

The PK parameter values for all subjects in the PK population (including those who vomited within 2 times the median Tmax) were similar to those obtained when subjects who vomited within 2 times the sodium oxybate median Tmax were excluded. Mean sodium oxybate Cmax values were 154 µg/mL and 152 µg/mL, mean AUC0-inf values were 323 µg·h/mL and 326 µg·h/mL, mean t1/2 values were 0.62 h and 0.63 h, and median Tmax values were 0.57 h and 0.50 h, for Treatments A and B, respectively.

The ratios of geometric mean sodium oxybate PK parameters Cmax and AUC0-inf for Xyrem prepared with a flavored diluent solution versus Xyrem prepared with water were 97.4% (90% CI of 88.6%–107.2%) and 101.3% (90% CI of 92.9%–110.3%), respectively (see Table 10 below).

Table 10. Statistical Analysis of Variance for Sodium Oxybate Pharmacokinetic Data Following a Single Dose of Sodium Oxybate in Flavored Diluent or Water (PK Completer Population)

Treatment Comparison	Parameter	Geometric LS Means [Back-Transformed]		% Ratio of Geometric Means	90% CI
		Treatment A (Test)	Treatment B (Reference)		
A versus B	C_{max}	146.52	150.38	97.4	88.6–107.2
	AUC_{0-t}	305.05	301.32	101.2	92.9-110.4
	AUC_{0-inf}	306.61	302.84	101.3	92.9–110.3

[a] Subjects (b) (6) were excluded from the statistical analysis of variance due to vomiting within 2 times the Xyrem median T_{max}.

Safety:

The overall safety profile was similar for both treatment groups. AEs were reported by 33 (100%) subjects receiving Xyrem prepared with flavored diluent and by 32 (97%) subjects receiving Xyrem prepared with water.

The most frequently reported AEs (incidence ≥10% of subjects overall) were somnolence, dizziness, nausea, snoring, vomiting, headache, euphoric mood, emotional disorder, feeling of relaxation, crying, and paresthesia. All AEs were of mild or moderate severity, and most were considered by the investigator to be related to study drug or procedure.

No deaths or other serious adverse events occurred during the study. One subject was discontinued because of a TEAE of anxiety following treatment with Xyrem prepared with flavored diluent in the first treatment period. The event was considered by the investigator to be mild and related to study drug or procedure.

No clinically significant trends were noted for laboratory test results, vital sign measurements, oxygen saturation values, or ECGs.

Conclusions:

Pharmacokinetic Conclusions: Xyrem prepared with a flavored diluent solution was found to be bioequivalent to Xyrem prepared with water with regard to peak (Cmax) and total (AUC) exposure after oral administration.

Safety Conclusions: The overall safety profile was similar for Xyrem prepared with flavored diluent and Xyrem prepared with water. AEs observed in this healthy subject population were consistent with AEs listed in the approved product labeling for Xyrem. No new safety issues were identified when Xyrem was prepared with flavored diluent.

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/s/

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