CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	212690 Sequence Number 0001
Link to EDR	\\CDSESUB1\evsprod\NDA212690\212690.enx
Submission Date	01/21/2020
Submission Type	505(b)(1) Application – Priority review
Brand Name	XYWAV™
Generic Name	JZP-258
Dosage Form and Strength	Solution (0.5 g/ml), for oral administration
Proposed Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Proposed Dose/regimen	Adults: Initiate dosage at 4.5 g per night orally divided into two equal doses taken 2.5 to 4 hours apart • Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later). • Recommended dosage range: 6 to 9 g per night orally. Pediatric patients (7 years of age and older) The recommended starting dosage, titration regimen and maximum total nightly dosage are based on body weight
Applicant	Jazz Pharmaceuticals Ireland Limited.
Associated IND	49641
OCP Review Team	Gopichand Gottipati Ph.D., Atul Bhattaram, Ph.D., Sreedharan Sabarinath, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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List of Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
AUCinf	AUC from time 0 to extrapolated to infinity
AUClast	AUC from time 0 to last measurable concentration
CI	Confidence intervals
Cmax	Maximum (peak) drug concentration
FDA	Food and drug administration
LLOQ	Lower limit of quantification
NDA	New Drug Application
PK	Pharmacokinetics
Tmax	Time of maximum (peak) drug concentration
USPI	United States package insert

1 Executive Summary

Jazz Pharmaceuticals Ireland Limited submitted this original 505(b)(1) New Drug Application (NDA 212690) seeking approval for XYWAV™ (JZP-258) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. JZP-258 is a 0.5 g/mL aqueous solution of mixture of calcium, potassium, magnesium, and sodium salts of oxybate; equivalent to 0.413 g/mL oxybate. Xyrem® (sodium oxybate) oral solution (also marketed by the same applicant) was approved by the Food and Drug Administration (FDA) for the treatment of cataplexy in narcolepsy (07/17/2002) and excessive daytime sleepiness (11/18/2005) in adults, and subsequently in pediatric patients 7 years and above for both indications (10/26/2018).

The proposed adult JZP-258 dosing recommendations are to initiate JZP-258 at 4.5 g per night orally in two equally divided doses taken 2.5 to 4 hours apart, and titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later), not exceeding total nightly dose of 9 g. The proposed JZP-258 pediatric dosing recommendations for initiation, titration regimen and maximum total nightly dosage are based on body weight. These recommendations are identical to those included in US package insert (USPI) for Xyrem®[1].

The application package includes two relative bioavailability/bioequivalence studies, 13-010 and JZP258-101, in healthy subjects comparing JZP-258 with Xyrem® and a phase 3 double-blind, placebo-controlled randomized withdrawal study (15-006) in adult patients with narcolepsy. In addition, population PK and exposure-response analyses were included in this submission. This NDA relies on the approved product Xyrem (also from the same applicant) for dosing recommendations for intrinsic and extrinsic factors.

The primary focus of this review is to evaluate the dosing recommendations for JZP-258 with regards to food-intake.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) recommends the approval of JZP-258 for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adult and pediatric populations at doses listed below. (b) (4) The first dose of JZP-258 should be administered at least 2 hours after meals, just as it is recommended in the USPI for Xyrem.

Key review issues with specific recommendations and comments are summarized below.

[1] USPI for Xyrem accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

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<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Evidence of effectiveness:</td><td>One double-blind, placebo-controlled, randomized-withdrawal, multicenter, phase 3 study (15-006) in patients with narcolepsy provided the primary evidence of effectiveness.

In this study patients were titrated to an optimal dose (administered as two equally divided nightly doses) of JZP-258 based on tolerability/efficacy over a 12-week open-label period and continued this stable dose for 2 weeks. Subsequently, they were randomized to either continue the stable dose or to placebo over a 2 week double-blind withdrawal period. Please refer to the clinical and biometrics reviews for more information.</td></tr>
<tr><td>General dosing instructions:</td><td>• The total nightly dose of JZP-258 is divided into two equal doses, and the patients should not take the second dose until 2.5 to 4 hours after the first dose.
• The total nightly dose of JZP-258 is gradually titrated based on efficacy and tolerability

The recommended adult XYWAV dose regimen (g = grams)
<table><tr><td>If a Patient's Total Nightly Dose Is:</td><td>Take at Bedtime:</td><td>Take 2.5 to 4 Hours Later:</td></tr><tr><td>4.5 g per night</td><td>2.25 g</td><td>2.25 g</td></tr><tr><td>6 g per night</td><td>3 g</td><td>3 g</td></tr><tr><td>7.5 g per night</td><td>3.75 g</td><td>3.75 g</td></tr><tr><td>9 g per night</td><td>4.5 g</td><td>4.5 g</td></tr></table>
The first dose of JZP-258 should be taken at least 2 hours after meals. A food-effect study indicated that oxybate PK is impacted by concomitant administration of JZP-258 with food. Additionally, the patients enrolled in pivotal phase 3 study were instructed to take JZP-258 at least 2 hours after meals, which is also consistent with the recommendation in USPI for Xyrem. Lastly, reviewer's independent population PK and exposure-efficacy analyses indicated that there could be a potential for loss of efficacy by 30-40% in cataplexy frequency and 10-20% in Epworth Sleepiness Scale when JZP-258 is taken with food.</td></tr>
</table>

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments

General dosing instructions:

Recommended initial XYWAV dosage for patients 7 years of age and older*

Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
<20 kg**	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to <30 kg	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 kg to <45 kg	≤1.5 g	≤1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥45 kg	≤2.25 g	≤2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

* For patients who sleep more than 8 hours per night, the first dose of XYWAV may be given at bedtime or after an initial period of sleep.

**If XYWAV is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

Review Issues	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	The dosing in patient subgroups based on intrinsic and extrinsic factors are identical to the recommendations provided in USPI for Xyrem. Please refer to the USPI of Xyrem for details.
Bridge between the "to-be-marketed" and clinical trial formulations	The commercial and clinical trial formulations are the same and therefore, no PK bridging studies were required.

1.2 Post-marketing Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

The information listed below is mostly based on the clinical pharmacology information provided in the USPI for Xyrem, except for the absorption section, which presents information relevant to JZP-258 from the relative bioavailability/food-effect studies.

Mechanism of Action:

Oxybate is a CNS depressant. The exact mechanism of action of JZP-258 in the treatment of narcolepsy is unknown. JZP-258 is a mixture of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate (gamma hydroxybutyrate). Gamma-Hydroxy Butyrate (GHB)[2] is an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of JZP-258 on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

[2] GHB and oxybate have been used interchangeably in this review

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Absorption

- Following oral administration of JZP-258 in healthy adults in fasted state, the average Tmax for GHB was about 1.3 hours.
- Following oral administration of JZP-258, the plasma levels of GHB increased more than dose-proportionally, with Cmax increasing approximately 2-fold and AUC increasing 2.9-fold as the dose was doubled from 2.25 g to 4.5 g. Single doses greater than 4.5 g have not been studied.
- Administration with food decreases exposures of GHB. Concomitant administration of JZP-258 with a standardized high fat meal resulted in a mean reduction in Cmax and AUC_{0-inf} of GHB by 33% and 16% respectively, while mean Tmax was unaffected. Concomitant administration of Xyrem with a standardized high fat meal resulted in a mean reduction in Cmax and AUC_{0-inf} of GHB by 44% and 19% respectively, and 0.36 hours delay in mean Tmax.

Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism and Excretion

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. No active metabolites have been identified.

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has a mean terminal elimination half-life of 0.66 hours.

Specific Populations

- Renal elimination is a minor pathway for GHB clearance. No dose adjustments are required based on renal function impairment.
- The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night administered orally, divided into two doses.
- Dosing in pediatric subjects ≥ 7 years is based on body weight.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The adult dosing recommendations for JZP-258 are consistent with instructions provided to patients enrolled in the phase 3 study as noted in Table 1-1 above. The pediatric dosing recommendations in patients ≥ 7 years are based on bodyweight such that the exposures match the adult exposures and based on extrapolating efficacy of JZP-258 from adults. These pediatric dosing recommendations are consistent with those included in USPI for Xyrem.

2.2.2 Therapeutic individualization

No clinical studies were conducted by the applicant to inform therapeutic individualization for JZP-258. Differences in the salt forms with the equivalent oxybate concentrations are not expected to result in changes in the impact of intrinsic/extrinsic factors relative to that following oral administration Xyrem®. Please refer to the recommendations included in the USPI for Xyrem®[3] for additional details.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology review team accepts the labeling concepts proposed by the applicant (b) (4) The review team recommends that the first dose of JZP-258 should be administered at least 2 hours after meals. Please refer section 3.3.4 for additional details.

[3] USPI for Xyrem accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

JZP-258 is a mixed salt formulation consisting of calcium, potassium, magnesium, and sodium salts of oxybate; equivalent to 0.413 g/mL oxybate. In late 2013, the applicant discussed their plans to pursue development of a low sodium alternative to Xyrem® oral solution (which is also a product of the same applicant) with the agency and proposed to conduct a Phase 1 relative bioavailability (BA)/bioequivalence (BE) and food effect study (13-010). The Agency agreed to waive the requirement to conduct a Phase 3 study to demonstrate safety/efficacy of JZP-258 contingent upon establishing BE between their product and Xyrem® oral solution.

In late 2015, at the end-of-phase 2 meeting, the applicant noted that the relative BA/BE study 13-010 (in which both the products were administered with 240 ml of water) met the BE criteria for $AUC_{0\text{-}inf}$ but not for Cmax (geometric mean ratio of JZP-258 to Xyrem: 74.2% [90% confidence interval: 67.8% – 81.2%]) under fasting conditions. The applicant also noted a similar outcome in another relative BA/BE study JZP258-101 (in which both the products were administered with 60 ml of water, which is the recommended volume per the package insert for Xyrem®): met the BE criteria for AUC0-inf but not for Cmax (geometric mean ratio of JZP-258 to Xyrem: 77.0% [90% confidence interval 71.9% - 82.6%]) under fasting conditions. At this meeting, there was a discussion between the applicant and the agency on the need for a phase 3 study, and an agreement was reached that no additional clinical pharmacology, or safety data are needed.

In late 2019, at the pre-NDA meeting, the agency agreed to the applicant's proposal to use data from relative BA/BE study 13-010 (which include dose levels 2.25 g and 4.5) and population PK analyses to describe the dose-proportionality of JZP-258 in adults and pediatric subjects. Furthermore, the agency agreed that a pediatric efficacy study will be waived if the efficacy findings of JZP-258 in adults are similar to those of Xyrem®. The efficacy of JZP-258 can then be extrapolated to pediatric population and have the same dosage recommendations as Xyrem® in pediatric patients ≥ 7 years.

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3.2 General Pharmacological and Pharmacokinetic Characteristics

Please refer to the general clinical pharmacology information included in the USPI for Xyrem®[4] for additional details on distribution, metabolism and excretion of GHB.

Table 3-1 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Oxybate (gamma-hydroxybutyrate [GHB]) is an endogenous compound and metabolite of the neurotransmitter gamma-amino butyric acid (GABA). GHB is known to act as a Central Nervous System (CNS) depressant and is hypothesized to exerts its effects at noradrenergic, dopaminergic neurons and thalamocortical neurons, mediated through $GABA_B$ actions during sleep.
QT prolongation	No QTc studies were conducted
General Information	
Healthy volunteers vs. patients	PK data was not collected in the pivotal phase 3 study (JZP-258-101) for JZP-258. Oxybate PK is not expected to be different between healthy volunteers and patients.
Dose proportionality	Following oral administration of JZP-258, the plasma levels of GHB increased more than dose-proportionally, with Cmax increasing 2-fold and AUC increasing 2.9-fold as the dose was doubled from 2.25 g to 4.5 g.
Accumulation	Minimal accumulation is expected with the recommended dosing regimen.
Absorption	
Tmax	The average time to peak plasma GHB concentrations was about 1.3 hours
Bioavailability	An absolute bioavailability study was not conducted with JZP-258. Following oral administration of Xyrem, the absolute bioavailability is about 88%. The absolute bioavailability of oxybate is not expected to be very different between JZP-258 and Xyrem.

[4] USPI for Xyrem accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

Food Effect	Both JZP-258 and Xyrem reported a reduction in exposure when administered with food. When JZP-258 was administered immediately after a standardized high fat meal, mean oxybate exposures C_{max} and $AUC_{0\text{-}inf}$ decreased by 33%, and 16% respectively and no change was noted in the average $T_{max.}$ When Xyrem was administered immediately after a standardized high fat meal, mean oxybate exposures C_{max} and $AUC_{0\text{-}inf}$ decreased by 44%, and 19% respectively and the average T_{max} was delayed by 0.36 hours. In the phase 3 clinical efficacy/safety study (15-006), the subjects were instructed to take the first dose of JZP-258 at least 2 hours after meals. This instruction is consistent with the recommendations included in the USPI for Xyrem.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of JZP-258 for the treatment of the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy was demonstrated in one phase 3 clinical study (15-006).

Study 15-006 was a double-blind, placebo-controlled, randomized-withdrawal, multicenter study (NCT03030599) in adult patients with narcolepsy. It consisted of 2 parts – part 1 consisted of a 12-week open-label optimized treatment and titration period followed by a 2 week stable dose period (SDP) and finally a 2 week double-blind randomized-withdrawal period (DB RWP); followed by part 2, an optional 24-week open-label extension period. The study enrolled 201 subjects, 18 – 70 years of age, with narcolepsy with cataplexy, and a baseline history of at least 14 cataplexy attacks in a typical two week period prior to any treatment for narcolepsy symptoms. Of the 201 subjects, 134 were randomized 1:1, either to continue treatment with JZP-258 or to placebo in the 2 week DB RWP. PK data were not collected in this study. The subjects were instructed to take the first dose of JZP-258 at least 2 hours after meals. This instruction is consistent with the recommendations in the USPI for Xyrem.

Twice-nightly doses of JZP-258 were administered in 99% (68/69) of patients and one patient received JZP-258 thrice-nightly. The total nightly dose of JZP-258 was administered in two equally divided doses in 90% (62/69) of patients. Unequal doses were administered in seven patients treated with JZP-258.

The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the

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Epworth Sleepiness Scale (ESS) score as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP. The results for study 15-006 met the pre-specified statistical criteria for both the primary and secondary efficacy endpoints and are summarized in Table 2 below. Please refer to statistical review by Drs. Xiaorong Yan and Kun Jin and clinical review by Dr. Ranjit Mani for additional details.

JZP-258 was not studied in a pediatric clinical trial. As noted in Section 3.1 above, the agency agreed to extrapolating efficacy/safety from adults to pediatric subjects ≥ 7 years, and that the same recommendations in USPI of Xyrem® in the pediatric subjects are recommended for JZP-258. This was based on similar efficacy in adults observed for Xywav and Xyrem using same dosage and regimen.

Table 2 Mean Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (ESS)

	Average Weekly Number of Cataplexy Attacks		ESS SCORE	
	Placebo (N = 65)	XYWAV (N = 69)	Placebo (N = 65)	XYWAV (N = 69)
Baseline (2 Weeks of the Stable Dose Period)				
Mean (SD)	7.2 (14.4)	8.9 (16.8)	12.6 (5.5)	13.6 (5.3)
Change from Baseline (2 Weeks of the Stable Dose Period) to the 2 Weeks of the DB RWP			Change from End of Stable Dose Period to End of DB RWP	
Mean (SD)	11.5 (24.8)	0.1 (5.8)	3.0 (4.7)	0.0 (2.9)
p-value	<0.0001		< 0.0001	

DB RWP = Double-blind Randomized-withdrawal Period; SD = standard deviation

Source: Adapted based on Summary of Clinical Overview.

3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

The proposed dosage recommendations for initiation, titration and maximum recommended daily dosages are acceptable in adult and pediatric populations. The adult regimen is identical to those evaluated in their pivotal phase 3 study where they demonstrated efficacy/safety by meeting the pre-specified statistical criteria for both primary and secondary efficacy endpoints. The review team recommends administering the first dose of JZP-258 at least 2 hours after meals, just as studied in phase 3. Please refer to Section 3.3.4 for more information.

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The pediatric dosing is based on matching exposures to adult exposures and extrapolating efficacy from adults. Additionally, as noted in section 3.3.1, the proposed dosage regimens are identical to those listed in the USPI for Xyrem® for both adult and pediatric populations.

No new major safety concerns were observed in study 15-006 relative to those reported in the package insert of Xyrem®. Overall, in the safety database, the most commonly reported AEs in part-1 of study 15-006 included headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting. Please refer to the clinical safety review by Dr. Ranjit Mani and for further details. In conclusion, we recommend the approval of the dosage regimens for JZP-258 in both adult and pediatric subjects ≥ 7 years.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic/extrinsic factors?

The applicant did not conduct any studies in this current program to evaluate the impact of intrinsic/extrinsic factors. Differences in the salt forms with the same equivalent amount of oxybate are not expected to result in changes in the impact of intrinsic/extrinsic factors relative to that following oral administration Xyrem®. Therefore JZP-258 will have same recommendations for intrinsic and extrinsic factors as with Xyrem. Please refer to the recommendations included in the USPI for Xyrem®[5] for additional details.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-Drug Interactions

Yes. In a food-effect study (JZP258-101), administration of JZP-258 with 60 ml water immediately after a high-fat meal resulted in a mean reduction in Cmax and $AUC_{0\text{-}inf}$ of GHB by 33% and 16% respectively and no change was noted in mean Tmax.

(b) (4)

[redacted]

[5] USPI for Xyrem accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

(b) (4)

The review team disagrees (b) (4) because of the following considerations:

1. Both JZP-258 and Xyrem showed reduction in exposure with food. (b) (4) the results from study JZP258-101 indicate that food-intake impacts the PK of oxybate following JZP-258 administration, though the magnitude of this impact of food-intake on oxybate PK following JZP-258 dosing was marginally lower compared to that following Xyrem dosing.
2. The USPI of Xyrem instructs administration of the first dose at least 2 hours after meals. The subjects enrolled in the pivotal Phase 3 study 15-006, were instructed to take JZP-258 at least 2 hours after meals, that is similar to the recommendation per USPI for Xyrem.
3. (b) (4)

4. The reviewer's analyses (described below in brief and in detail in Section 4.2.3) under the 'worst-case' scenario indicated that the magnitude of the impact of food-intake on potential loss of efficacy is larger than the applicant's analyses.

The reviewer's independent analyses suggested that the estimate for potential loss of efficacy in TCAT is 30-40% and ESS scores is 10-20% due to decrease in Cmax following first dose of JZP-258 when taken with food under the worst-case scenario noted above. These estimates are generally comparable to the estimates for potential loss of efficacy (20-40% for TCAT and 10-20% for ESS score) provided by the applicant under the worst-case scenario in response to information request (received 05/21/2020) [Please refer to Appendix 4.2 for additional details].

Briefly, the reviewer noted that the popPK model characterized the observed data reasonably and therefore, it is considered acceptable. Next, plasma-concentration profiles based on bodyweight and food-intake status following 4.5 g in equally divided doses administered 4 hours apart: JZP-258 and Xyrem under fed and fasted conditions respectively. Subsequently, exposure-efficacy analyses were conducted using the popPK derived exposures, summarized by Cmax following the first dose and primary efficacy endpoints – TCAT and ESS score from parallel-group design studies OMC-GHB-02 and/or OMC-SXB-15 (please refer to appendix 4.2 for additional considerations regarding study designs and rationale for selecting these studies]. The results for reviewer's analyses are shown below.

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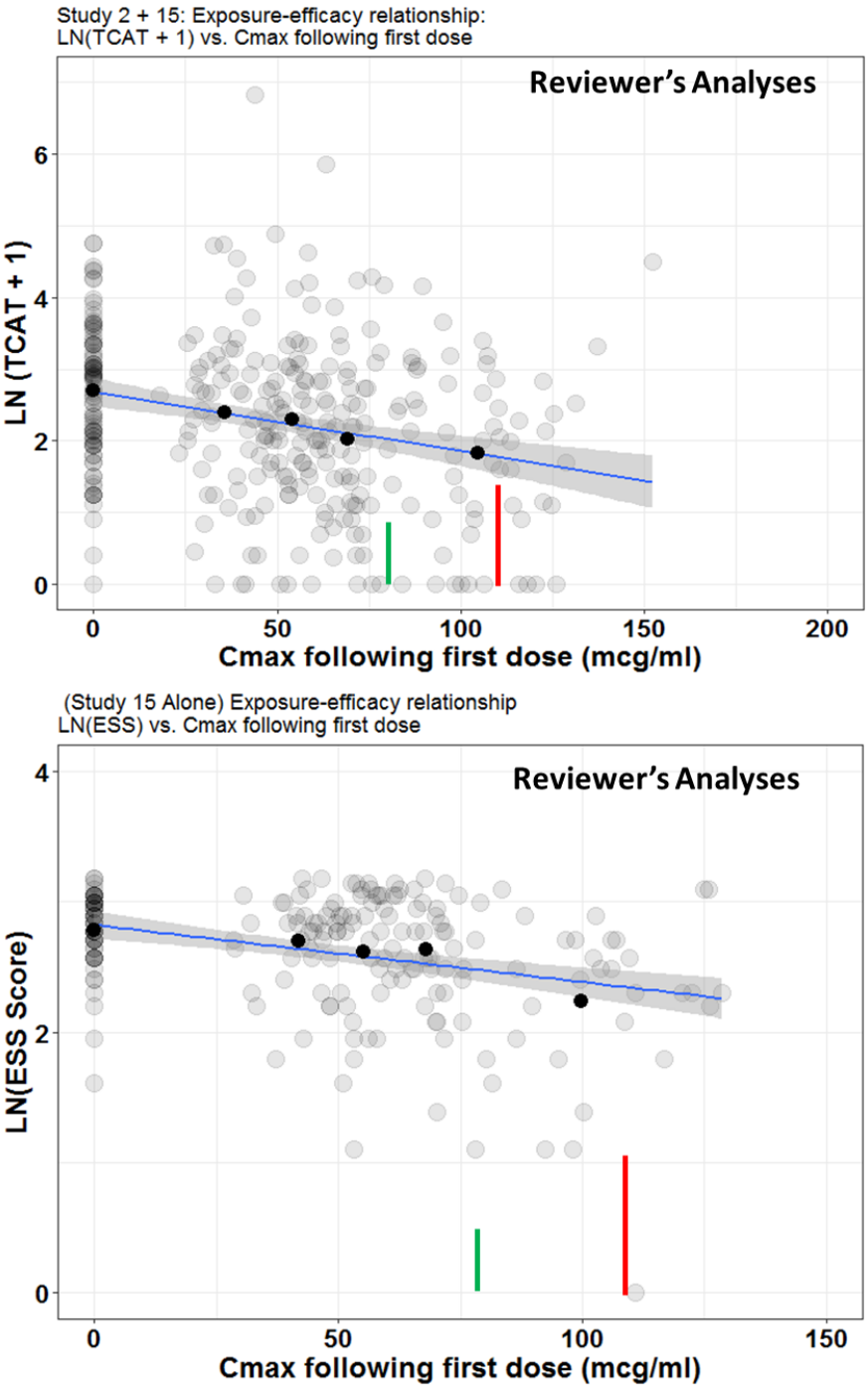
Figure 1 Exposure-efficacy analyses conducted by the reviewer to evaluate the impact of food-intake on exposures and potential loss of efficacy in primary efficacy endpoints



**Study 2 – OMC-GHB-02; and Study15 - OMC-SXB-15;*

Note: Red vertical line represents Cmax following first dose of 2.25 g of Xyrem in fasted state and green vertical line represents Cmax following first dose of 2.25 g of JZP-258 in fed state, both derived based on popPK model

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The reviewer noted minor discrepancies with the applicant's exposure-efficacy analyses (i.e., slope of the relationships) and sent information requests (IR) to verify the applicant's analyses. Based on the responses to IR, the applicant noted that the magnitude of the potential for loss in efficacy in cataplexy frequency by 22% and in ESS score by 12%, while the reviewer's analyses indicated that these estimates were 27% and 13% for cataplexy frequency and ESS score respectively.

Though the popPK model was considered reasonable in characterizing the general trends and variability in the observed data, there were minor inconsistencies in predicting the Cmax following the first dose as noted in tables below. Therefore, the reviewer also estimated the potential loss of efficacy in TCAT and ESS scores using the observed data in addition to the popPK derived metrics and the review team considered these values in providing the final recommendations.

Table 3 Estimates for potential loss of efficacy in TCAT based on pooled data from studies OMC-GHB-02 and OMC-GHB-15

Study	Cmax following first dose: JZP-258 fed vs. Xyrem fasted [mcg/ml]	Reviewer's Analyses	Applicant's Analyses
PopPK model-derived	78.5 vs. 111.6	27%↓	22%↓*
JZP258-101	62.3 vs. 120.2	43%↓	37%↓**

** Estimate based on applicant's response to IR received 05/21/2020; **Estimated by reviewer based on applicant's response to information request*.

Table 4 Estimates for potential loss of efficacy in ESS based on data from study OMC-GHB-15

Study	Cmax following first dose: JZP-258 fed vs. Xyrem fasted [mcg/ml]	Reviewer's Analyses	Applicant's Analyses
PopPK model-derived	78.5 vs. 111.6	13%↓	12%↓*
JZP258-101	62.3 vs. 120.2	22%↓	20%↓**

** Estimate based on applicant's response to IR received 05/21/2020; **Estimated by reviewer based on applicant's response to information request*.

Please refer to section 4.2.3 for further details regarding methods and additional considerations.

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3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Yes, the dosage form and strength of the commercial to-be-marketed formulation (oral solution) is the same as the formulation used by the applicant in their pivotal phase 3 study (15-006).

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

Plasma concentrations of oxybate were determined using a validated liquid chromatography (LC) – tandem mass spectrometry (MS/MS) detection method. The linearity range was 0.750 – 192 µg/mL. The bioanalytical method study report is referenced from Study No. BJAZZ1602P1 and the assay performance characteristics for the relative BA/BE study JZP258-101 are summarized below:

Key Features	Acceptance Criteria	Method Performance
Linearity		
Weighting	—	$1/x^2$
Bias at LLOQ	± 20.0% Bias	-1.8%
Bias above LLOQ	± 15.0% Bias	-4.8 to 3.9%
Bioanalytical range	0.750 to 192 µg/mL	Complies
Precision		
Intra-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	6.4 to 13.2% (LLOQ); 0.9 to 4.7% (above LLOQ)
Inter-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	11.5% (LLOQ); 2.9 to 3.8% (above LLOQ)
Accuracy		
Intra-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	1.5 to 12.5% (LLOQ); -3.4 to 5.7% (above LLOQ)
Inter-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	8.5% (LLOQ); -0.9 to 3.9% (above LLOQ)
Dilution (2×, 5×)		
Precision	≤ 15.0% CV	1.9%, 3.6%
Accuracy	± 15.0% Bias (above LLOQ)	0.4%, -2.8%

%CV = percent coefficient of variation; IS = internal standard; LLOQ = lower limit of quantification

Source: Summary of Clinical Pharmacology Studies report – Table 3 on page 7

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4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Applicant's Population PK analysis:

Population PK (PopPK) analyses were conducted by the applicant to characterize the PK of JZP-258 in healthy subjects and patients with narcolepsy associated with cataplexy. Their key objectives were to: (1) characterize the effects of intrinsic and extrinsic factors on the PK of JZP-258 that can potentially explain the interindividual differences in PK and aid in appropriate dose adjustment if necessary; and (2) derive exposure metrics that can be used for subsequent exposure-response analyses of efficacy and safety endpoints.

Data from 6 clinical studies were used in the population PK analyses and a brief description of these studies is given in Table 5.

Table 5 Summary of the characteristics of the studies used for PopPK analyses

	Study design and patient population (PK evaluable population)	Dosing regimen	Blood sample collection
OMC-SXB-9 Xyrem	Open-label, two-period, two treatment, crossover randomized study *Healthy subjects (N=13)*	2 doses of 2.25 g, or 2 doses of 4.5 g administered 4 hours apart, On study days 1, 8 1st dose 2 hours after evening meal, Bed-time for 1st dose and 4 hours later	Pre-dose, 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, 10 hours after the first dose
09-002 Xyrem	Open-label, randomized, relative bioavailability (of sustained release tablet vs. oral solution), crossover randomized study *Healthy subjects (N=59)*	*Only oral solution data:* 2 doses of 3 g administered 4 hours apart 1st dose in the morning, after an overnight fast	Pre-dose, 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 the first dose.
OMC-SXB-10 Xyrem	Open-label, two-period, comparing single dose vs. 8-week dosing *Narcoleptic adults (N=13)*	4.5 g every night for 8w 1st dose 2 hours after evening meal, Bed-time for 1st dose and 4 hours later	Pre-dose, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 hours after each of two 4.5 g doses

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13-005 Xyrem	Double-blind, placebo-controlled, randomized-withdrawal study in peds with narcolepsy with cataplexy (N=28) PK data from subset of patients only	Titration of Xyrem-naïve patients to a stable nightly dose or Stable nightly dose of patients already Xyem (steady-state dosing) 1 – 4.5 g BID; 1st dose 2 hours after evening meal, Bed-time for 1st dose and 4 hours later	Pre-dose, 0.75, 1.5, 4, 4.75 and 8 hours after first dose
13-010 Xyrem, JZP-258	Open-label, randomized, crossover study for relative BA/BE, food-effect *Healthy subjects (N=60)*	Xyrem: 4.5 g, JZP-258: 2.25 g and 4.5 g Daytime Fasted: Following overnight (10 hours) fast and 4 hours after dosing Fed: immediately after high-fat, high meal	Pre-dose, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours after the administration
JZP258-101 Xyrem, JZP-258	Open-label, randomized, crossover study for relative BA/BE, food-effect, and dosing volume *Healthy subjects (N=48)*	Xyrem: 4.5 g, JZP-258: 4.5 g Daytime Fasted: Following overnight (10 hours) fast and 4 hours after dosing Fed: immediately after high-fat, high meal	Pre-dose, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours after the administration

Note: N: Number of subjects included in the respective trials;
Source: Adapted from the PopPK report, Tables 1, 2, and 3 on pages 28 and 32

The final dataset for PopPK analyses consists of a total of 9373 quantifiable GHB plasma concentrations from a total 222 subjects, which also included pediatric subjects from Xyrem program. The PK data for Xyrem from all the studies except JZP258-101 were used for developing PopPK model in the previous submission of Xyrem in pediatric patients. It was previously reviewed by the clinical pharmacology review team (DARRTS 10/23/2018) and noted that the model appeared to provide an adequate description of the time course of oxybate concentrations following administration of Xyrem.

In the current submission, PK of oxybate following JZP-258 administration from studies 13-010 and JZP258-101 and PK of oxybate following Xyrem administration from study JZP258-101 was

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added to the dataset included in the previous analyses. The PopPK data of JZP-258 was modeled using non-linear mixed effects in NONMEM. The structural model was based on previously developed PopPK model and consists of a two-compartment model with first-order absorption with a lag time and Michaelis - Menten non-linear clearance. Absorption was characterized by a first-order absorption rate constant (ka, hr^{-1}), and an absorption lag was noted, characterized by series of absorption transit compartments (N) and mean transit time (MTT). Distribution was characterized by apparent volume of distribution of central compartment (Vc/F, L) and peripheral compartment (Vp/F, L), and elimination characterized by intercompartmental clearance (Q/F) and Michaelis - Menten non-linear clearance parameters – Vmax/F and km.

Covariate identification was performed in a step-wise manner and the list of covariates explored are summarized in Table 6 below.

Table 6 List of covariates explored in population PK analyses

Parameter	Covariates
Vmax/F, Km	age, weight, BSA, sex, race, ethnicity, ALB, ALT, AST, BILI, patient/healthy, CrCL, dose (g and mg/kg)
Volume of Distribution (Vc/F, Vp/F)	weight, BSA, race, sex, patient/healthy
MTT, N, ka	Age, sex, food, formulation, dose (g and mg/kg)

Note: ALB-albumin; ALT-alanine aminotransferase; AST-asparagine aminotransferase; BILI-bilirubin; BSA-body surface area; Vmax/F and km- Michaelis-Menten nonlinear clearance terms; CRCL-creatinine clearance; Vc/F-central volume of distribution, g – grams; mg/kg – milligrams per kilograms; ka – absorption rate; MTT - mean transit time; N - number of transit compartments; Vp/F – peripheral volume of distribution .
Source: Oxybate Population PK Analysis Report – Table 6, Page 40

It was noted that bodyweight-BSA; bodyweight-age were highly correlated, and the choice of the best predictor was guided by the prior PopPK analyses, and bodyweight was ultimately retained on Vmax/F and Vc/F. Food and formulation were retained as covariates on each of ka and MTT.

The parameter estimates of the final PopPK model along with their precision (nonparametric stratified bootstrap analysis) are shown in Table 7. Furthermore, the qualification of the final popPK model was performed using goodness of fit diagnostics and visual predictive checks shown in Figure 2 and Figure 3 respectively. The applicant also conducted simulations for twice nightly dosing of 4.5 gm of Xyrem and JZP-258 separated by 4 hours under fed and fasted conditions and is shown in Figure 4 for reference.

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Table 7 Parameter estimates of the final PopPK model

Parameter (Units)	Model Parameter	Estimate	SE NM (%CV)	SE BS (%CV)
Vmax/F (L/hr)	θ_1	1845 [a]	1.1	6.4
Body Weight on Vmax/F	θ_9	0.609	10.4	9.2
km (µg/mL)	θ_2	14.2 [a]	3.4	5.4
Vc/F (L)	θ_3	39.3 [a]	2.8	6.1
Body weight on Vc	θ_{10}	0.782	7.1	7.0
Vp/F (L)	θ_4	8.8 [a]	5.0	5.9
Q/F (L/hr)	θ_5	5.2 [a]	15.4	10.2
ka (/hr)				
Fasted JZP-258	θ_6	3.6 [a]	5.5	8.3
Fed JZP-258	θ_{14}	1.8 [a]	<.1	7.5
Fasted Xyrem	θ_{11}	16.1 [a]	26.1	14.2
Fed Xyrem	θ_{15}	1.8 [a]	<.1	6.3
MTT (minutes)				
Fasted JZP-258	θ_{12}	10.5 [a]	8.7	6.4
Fed JZP-258	θ_{16}	2.2 [a]	<.1	18.9
Fasted Xyrem	θ_{13}	14.0 [a]	31.3	4.4
Fed Xyrem	θ_8	4.9 [a]	<.1	10.5
N (compartments)	θ_7	4.6 [a]	6.2	6.0
Residual Error (%CV)	σ	20.2	5.3	5.1
Inter-individual variability (IIV)				
Vmax/F	Ω_1	42.9	6.2	4.4
km	Ω_2	52.9	7.9	5.5
Vc/F	Ω_3	17.0	7.2	7.8
Vp/F	Ω_4	15 [d]	0 [d]	0 [d]
Q/F	Ω_5	15 [d]	0 [d]	0 [d]
ka	Ω_6	66.3	12.6	5.6
MTT	Ω_7	72.5	5.6	5.3
N	Ω_8	83.8	9.3	9.4

Source: ..\jazz\xyrem\final\final.nm7\final.smr and ..\jazz\xyrem\dev\final\sasout\bootstrap\parmsout.rtf

[a]anti-log of estimated parameter; [b]Standard error of the log transformed, estimated parameter; SE NM – NONMEM standard error estimate; SE BS – Bootstrap standard error estimate; IIV - inter-individual variability; L-liters; hr - hour; Vmax/F – apparent maximal elimination rate; km – apparent concentration at half-maximal elimination, a Michaelis-Menton constant; Q/F - apparent inter-compartmental clearance; Vc/F-central volume of distribution; Vp/F - peripheral volume of distribution; ka – absorption rate constant; N – number of transit compartments; MTT – mean transit time; CV – coefficient of variation; µg/mL – micrograms milliliter

Source: Population PK report Table – 8 on Page 56

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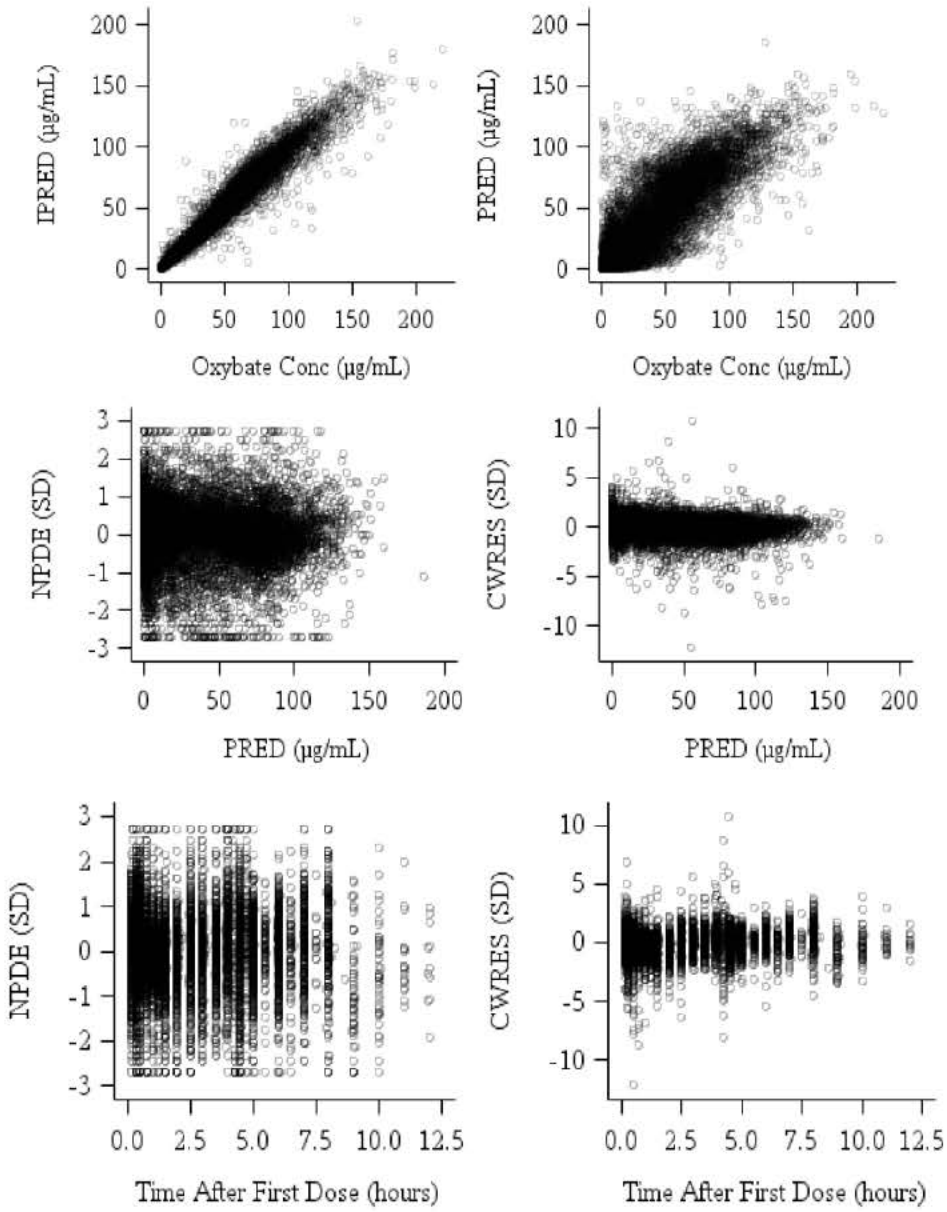
Figure 2 Goodness of fit plots for the final PopPK model – predictions (top panel) and residuals (bottom panel)



Note: IPRED: Individual prediction (mcg/mL), PRED: Population prediction (mcg/mL); NPDE: Normalized prediction distribution errors, CWRES: Conditional weighted residuals
Source: Population PK report Figures 15-17 on Pages 57 & 58

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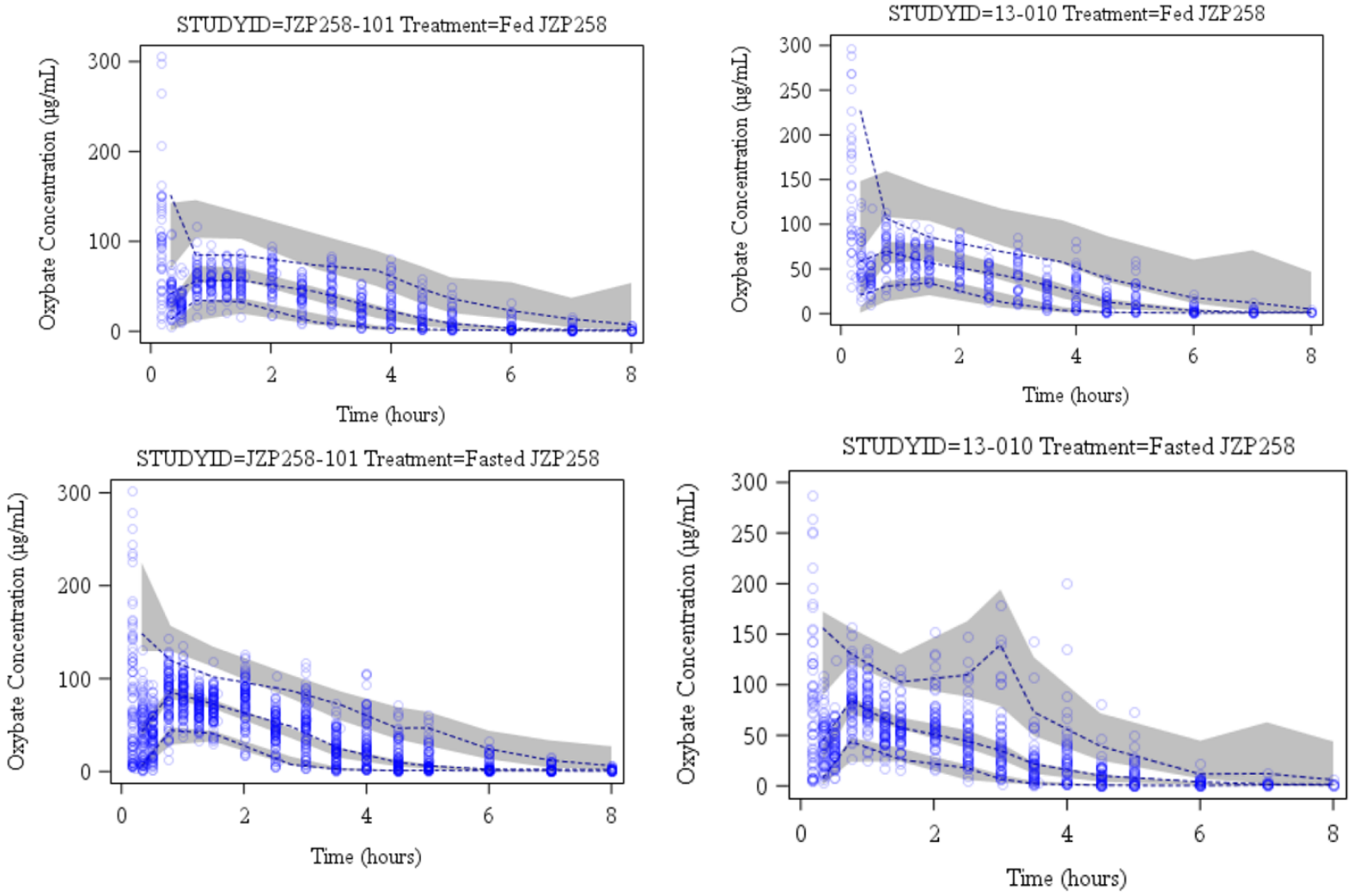
Figure 3 Visual predictive check of the final popPK model



Source: Population PK report Figure 24, 26, 28, 30 on Page 63-66

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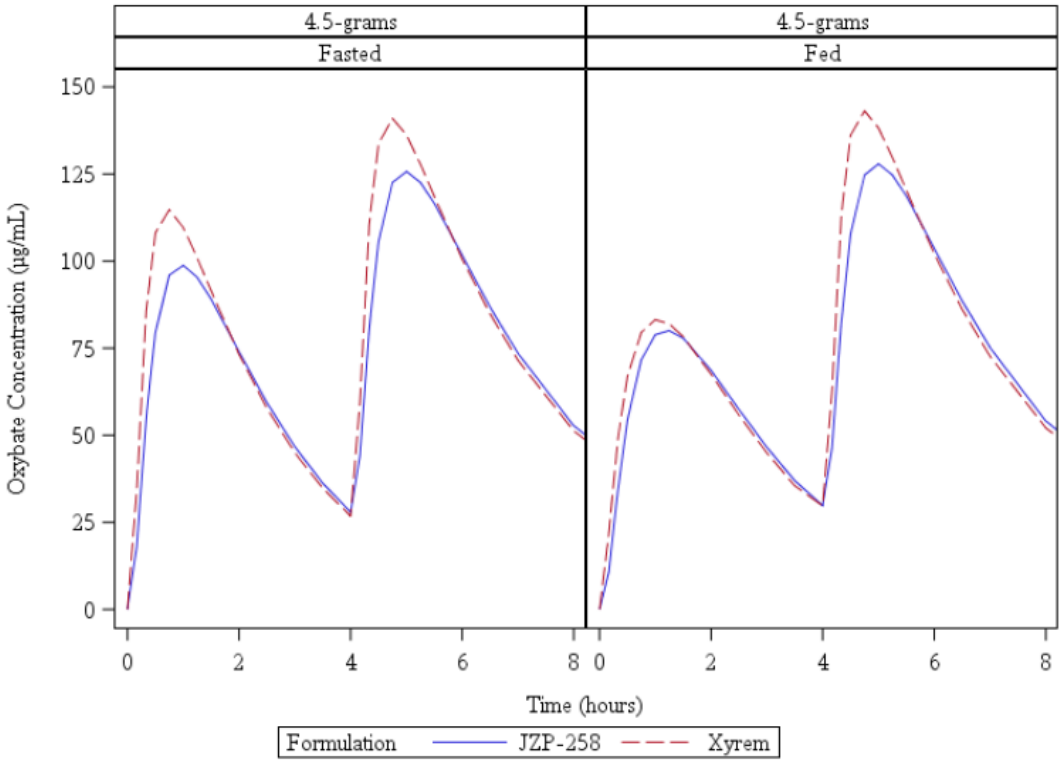
Figure 4 JZP-258 and Xyrem twice nightly dosing profiles following 4.5 gm dosing separated by 4 hours



Source: Population PK report Figure 41 on Page 83

Reviewer's comments:

The applicant's popPK analysis is consistent with the previously developed popPK model and is generally aligned with previous knowledge of oxybate kinetics. Specifically, the current analyses found the bodyweight was a significant covariate impacting oxybate PK, while food-effect and formulation impacted absorption parameters (ka and MTT). These relationships are plausible based on the observed data (e.g., food-effect and formulation on absorption) and the simulated PK data were also consistent with the observed data (e.g., more than dose-proportionality for AUC). Though bodyweight was reported as a significant covariate, given that JZP-258 dose is titrated based on tolerability and efficacy, fixed-dosing is acceptable in adults, while in pediatric patients ≥ 7 years, dosing should be based on bodyweight (similar to that in Xyrem). Overall, the population PK model adequately characterized the observed data reasonably, capturing the trends and the popPK model parameters were reasonably precisely estimated and generally plausible. However, minor inconsistencies in predicting the Cmax following the first dose relative to the observed data were noted. The reviewer conducted independent analyses, specifically evaluating the diagnostics and generally considers the popPK model acceptable.

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4.2.2 Applicant's Exposure-Efficacy Analyses

Exposure-efficacy analyses were conducted by the applicant to explore the relationships between popPK derived exposure metrics (Cmax, AUC) of oxybate and efficacy endpoints cataplexy frequency (TCAT), ESS scores using data from both Xyrem and JZP-258 programs. Their key objectives were to (1) provide supportive evidence to support similar dose regimens for JZP-258 as approved for Xyrem in pediatric patients ≥ 7 years and adult patients with narcolepsy, and (b) (4)

Applicant conducted E-R analyses separately for parallel-group designs and randomized-withdrawal designs. PK data was not collected from any of the efficacy studies of Xyrem or JZP-258, except for a small subset of subjects (28/653) in study 13-005. Data from 6 clinical studies were used in the E-R analyses and a brief description of these studies is given in Table 8

Table 8 Key study features for studies used for exposure-response analyses

Design	Study	Regimen	Efficacy endpoints (Data count = N)
Randomized parallel-group designs	OMC-GHB-02	Xyrem: 0, 3-, 6-, 9-grams/day for 4 weeks	TCAT (N=136), ESS (N = 136)
	OMC-SXB-15	Xyrem: 0, 4.5-, 6-, 7.5-, 9-grams/day for 8 weeks	TCAT (N = 206), ESS (N = 206)
	OMC-SXB-22	Xyrem: 0, 6-, 9-grams/day for 4 weeks	ESS (N = 55)
Randomized withdrawal designs	OMC-SXB-21	Xyrem: Stable dose for 2-weeks then randomized to continue stable dose or placebo for 2-weeks	TCAT (N = 55)
	13-005	Xyrem: Stable dose for 2-weeks then randomized to continue stable dose or placebo for 2-weeks	TCAT (N=94), ESS (N = 93)
	15-006	JZP-258: Stable dose for 2-weeks then randomized to continue stable dose or placebo for 2-weeks	TCAT (N=134), ESS (N = 134)

Source: Adapted based on Tables 2, 7 on pages 46 and 59 in exposure-response analyses report

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In response to the information request received on 05/14/2020, the applicant noted that though the Intent-To-Treat (ITT) population generally included patients who had baseline, and at least one post-baseline visit, subjects who terminated the study early were not included in the final E-R analyses to avoid bias associated with imputing the endpoints. They also noted that using last observation carried forward method or other method of imputation when only baseline or early observation values are available would inappropriately underestimate the E-R response due to the time required to achieve a full response.

As noted above, since PK data was not collected in any efficacy study except for a small PK subgroup in 13-005, the final popPK model was used to derive plasma concentration-time profiles. Briefly, the subject's bodyweight (which was a significant covariate in the popPK model), food-intake and formulation were used as covariates to simulate PK profiles and derive exposure metrics – Cmax following first and second doses, AUCinf, 8-hour post first-dose concentrations.

In response to the information request received on 05/14/2020, the applicant noted that there were several cataplexy values of 0, and therefore a value of 1 was added to all values prior to log-transformation for the regression analyses, while ESS values were evaluated without adding 1 as they were not log-transformed.

For randomized parallel-group trials, linear, Emax models were evaluated for exposure metrics such as fixed dose (g), weight-normalized dose (mg/kg), Cmax and AUC0-inf. Model selection criteria was based on Akaike information criterion (AIC)and Bayesian information criteria (BIC). The significance of age, weight, sex and race as covariates were also evaluated.

For randomized withdrawal trials, formulation, age category effects were evaluated by ANOVA using models that included either AUC0-inf, Cmax and weight based (mg/kg) dose quartiles as main effects. An interaction term was included to assess the effects of formulation or age category by exposure quartile.

The results for the randomized parallel-group trials indicated linear regression was considered acceptable for all the exposure metrics evaluated as Emax model showed no apparent improvement in fit and no covariates were included in the final model. The results for Cmax and AUC0-inf for parallel-group trials for TCAT and ESS are shown in Table 9 and Table 10 below.

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Table 9 Final Exposure-Efficacy model using Cmax (top panel) and AUC0-inf (bottom panel) for TCAT

Parameter	Estimate	Standard Error	DF	Lower	Upper
Intercept	2.65050	0.10295	328	2.5049	2.8927
Slope	-0.00557	0.00182	328	0.002497	0.008789

Source: ..\nonmem\jazz\xyrem\dev\er\tcat.sas: cmax model summary.rtf
Cmax – maximum concentration, DF – degrees of fredom

Parameter	Estimate	Standard Error	DF	Lower	Upper
Intercept	2.6229	0.03349	328	2.4557	2.8015
Slope	0.000956	0.3641	328	0.000467	0.001957
Residual Error	3.4967	0.09775	328	2.8850	4.2381

Source: ..\nonmem\jazz\xyrem\dev\er\tcat.sas: auc model summary.rtf
AUC(0-∞) = area under the concentration-time curve extrapolated to infinity, DF – degress of freedom

Source: Exposure-response report - Tables 16, 19 on pages 68 and 71

Table 10 Final Exposure-Efficacy model using Cmax (bottom panel) and AUC0-inf (top panel) for ESS scores

Parameter	Estimate	Error	t-value	p-value
Intercept	16.244972	0.405712	40.04	<.0001
AUC(0-∞) (µg*hr/mL)	-0.010899	0.001481	-7.36	<.0001

Source: ..\Jazz\xyrem\dev\er\ess.sas: auc demog anova.rtf
ESS - Epworth Sleep Scale, AUC(0-∞) = Area under the concentration-time curve extrapolated to infinity, µg – micrograms, hr – hour, mL - milliliter

Parameter	Estimate	Error	t-value	p-value
Intercept	16.6733	0.4443	37.53	<.0001
C_{max} (µg/mL)	-0.0480	0.0064	-7.46	<.0001

Source: ..\Jazz\xyrem\dev\er\ess.sas: cmax demog anova.rtf
ESS = Epworth Sleep Scale, C_{max} = Maximum plasma oxybate concentration, µg – micrograms, mL – milliliters

Source: Exposure-response report - Tables 44, 47 on pages 100 and 103

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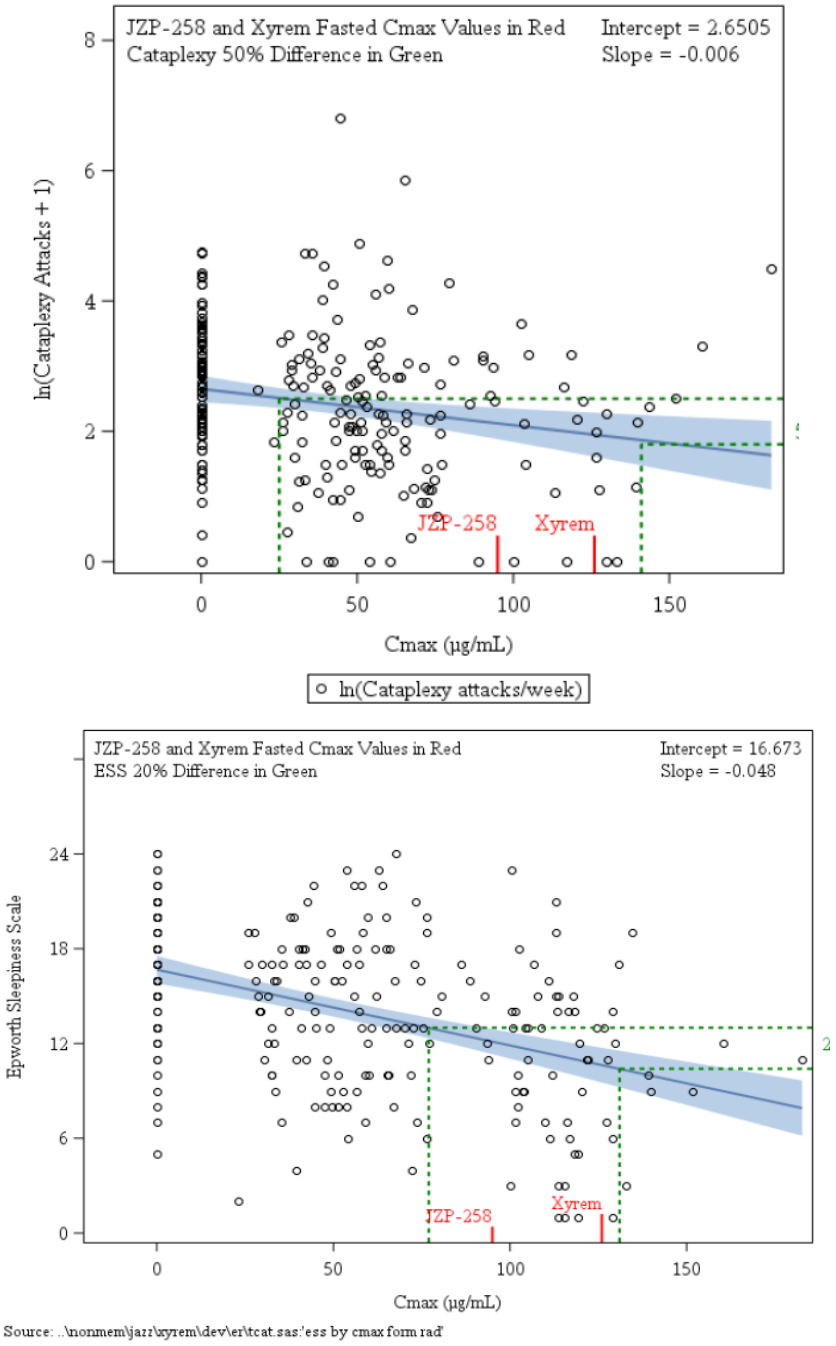
The applicant used the exposure-efficacy relationship for Cmax to evaluate the impact of the reduced exposures following food-intake on potential loss of efficacy in TCAT and ESS scores. As noted in section 3.3.1, the applicant noted that the results from the relative BA/BE studies, which failed to meet BE criteria for Cmax, showed that the Cmax following administration of JZP-258 was ~20% lower than that following Xyrem administration under fasting conditions. Additionally, the results for the impact of food-intake with JZP-258 on GHB PK showed a 20% lower Cmax in fed relative to fasted state.

The applicant noted that based on the E-R noted above, ~20% difference in Cmax translates to a potential loss of efficacy in TCAT by ~5% and in ESS score by ~14% (please refer to Figure 5 below for the exposure-efficacy relationship of TCAT and ESS on Cmax). (b) (4)

The applicant noted the E-R relationships were not apparent for either Xyrem or JZP-258 in the randomized withdrawal studies between the optimum effective dose/exposures and response measured as change from the optimal response associated with the stable-dose to lower response associated with placebo (no drug exposure). However, the results from these studies did show decline in efficacy from the optimal response associated with the optimal stable doses/exposures to lower responses associated with 2-week placebo treatment.

Figure 5 Exposure-Efficacy relationship of TCAT (top panel) and ESS (bottom panel) on Cmax – randomized parallel group trials



Source: Figures 7, 28 on pages 72 and 103 in exposure-response analyses report

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Reviewer's comments:

The applicant's approach in using popPK derived exposure metrics for conducting E-R analyses is reasonable. Though the applicant noted in their report that all the subjects randomized in the listed studies (Table 8) for E-R analyses, the sample sizes based on the individual clinical study reports did not match those used in the applicant's E-R analyses. Additionally, it was unclear from the report which Cmax was used for the E-R analyses, i.e., the one following the first/second dose. Lastly, the data treatment in terms of adding value of 1 to TCAT and/or ESS values was not clear in the original report. Consequently, an information request was sent to the response seeking clarifications on these issues. The applicant's response (dated 05/14/2020) noted that the subjects who terminated the study early were not included in the final E-R analyses to avoid bias associated with imputing the endpoints. They also noted that using last observation carried forward method or other method of imputation when only baseline or early observation values are available would inappropriately underestimate the E-R response due to the time required to achieve a full response. The applicant noted that the highest Cmax was considered for E-R analyses, which reflects following second dose; and that a value of 1 was added only TCAT prior to log-transformation.

In order to evaluate the decrease in exposures owing to the impact of food-intake (JZP-258 vs. Xyrem under fasting conditions) on potential loss of efficacy, the review team sent an additional information request: 1. to evaluate the potential loss of efficacy by using the Cmax following the first dose (because food-intake is only relevant to the first dose), comparing JZP-258 under fed condition and Xyrem under fasting condition (as it is more reflective of 'worst-case' scenario), and 2. to conduct E-R analyses using data from study OMC-SXB-15 alone and pooled data for randomized parallel-group studies separately for TCAT and ESS score. The applicant's response (dated 05/21/2020) addressed by including the estimates based on the 'worst-case' scenario using Cmax following first dose of JZP-258. The revised estimates based on applicant's analyses for potential loss of efficacy under the worst-case scenario for pooled data from studies OMC-GHB-02 and OMC-SXB-15 for TCAT was 22%, while potential loss of efficacy under the worst-case scenario for pooled data from studies OMC-GHB-02, OMC-SXB-15 and OMC-SXB-22 for ESS score was 15%. Additionally, the reviewer also noted that there 6 subjects (ID: (b) (6) (b) (6)) who had missing TCAT data (either baseline or endpoint visits) and were supposed to be excluded from the analyses based on applicant's analysis plan, these subjects were included in the dataset used to conduct E-R analyses received in response to IR (dated 05/21/2020).

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4.2.3 Reviewer's Exposure-Response Analyses:

Introduction

The [redacted] (b) (4) for JZP-258 as it relates to food-intake was based on their E-R analyses to translate the reduction in exposures to potential loss of efficacy for TCAT and ESS score under a 'worst-case' scenario. The reviewer conducting these analyses independently, in light of some discrepancies in the sample sizes used in applicant's E-R analyses as noted above and its potential implications on the applicant's estimates for the potential loss of efficacy. Briefly, first, popPK model-based simulations were conducted to derive exposures, i.e., Cmax following first dose of JZP-258 under fed conditions and Xyrem under fasted conditions for each subject in the parallel-group trials. Next, E-R analyses were conducted as originally conducted by the applicant, to quantify the impact of reduction of Cmax under worst-case scenario as noted above on the potential loss of efficacy in TCAT and ESS scores. For the purpose of these analyses, only data from studies OMC-GHB-02 and OMC-GHB-15 were considered appropriate and OMC-GHB-22 was excluded because the baseline period consisted of background therapy of modafinil.

Objective

- To evaluate the impact of food-intake on PK and translate the reduction in Cmax following first dose under the worst-case scenario to potential loss of efficacy and ESS score from appropriate parallel-group design studies
- Additionally, to evaluate this impact based on the observed PK data from study JZP258-101.

Datasets

Datasets used for the analyses are summarized in

Study Number	Name	Link to EDR
OMC-GHB-02	jazzer.xpt	\\cdsesub1\evsprod\nda212690\0001\m5\datasets\exposure-response\analysis\legacy\datasets\jazzer.xpt
OMC-SXB-15		

Software

The software tools used for this analysis include NONMEM (version 7) and R version (3.3.1) were utilized for dataset compilation, analyses and generation of plots.

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Methods

A dataset was set up for simulation of PK data for all the subjects from studies OMC-GHB-02 and OMC-GHB-15, and the final popPK model was used to simulate oxybate plasma concentrations-time profiles based on individual's bodyweight following administration of total nightly dose of 9 g of Xyrem in two equally divided doses separated by 4 hours. Only Cmax following the first dose is considered in the context of evaluating the impact of food-intake. Linear regression analyses of log-transformed TCAT data (by adding value of 1 to all subjects) from both studies and log-transformed ESS data from study OMC-GHB-15 was conducted in a similar methodology as described previously.

Results

The results for the potential loss of efficacy in TCAT based on pooled data from studies OMC-GHB-02 and OMC-GHB-15 are shown in Table 11 and in ESS score based on data from study OMC-GHB-15 in Table 12 below. Overall, the reviewer's analyses showed generally comparable estimates on potential loss for efficacy in TCAT and ESS scores relative to the estimates from the applicant's analyses, although values for TCAT were slightly higher potentially impacted due to the exclusion of 6 subjects as noted previously. The estimates based on the observed PK data from study JZP258-101 indicated that the potential loss of efficacy in TCAT and ESS scores may be higher.

Table 11 Estimates for potential loss of efficacy in TCAT based on pooled data from studies OMC-GHB-02 and OMC-GHB-15

Study	Cmax following first dose: JZP-258 fed vs. Xyrem fasted [mcg/ml]	Reviewer's Analyses	Applicant's Analyses
PopPK model-derived	78.5 vs. 111.6	27%↓	22%↓*
JZP258-101	62.3 vs. 120.2	43%↓	37%↓**

** Estimate based on applicant's response to IR received 05/21/2020; **Estimated by reviewer based on the estimates from applicant's response*.

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Table 12 Estimates for potential loss of efficacy in ESS based on data from study OMC-GHB-15

Study	Cmax following first dose: JZP-258 fed vs. Xyrem fasted [mcg/ml]	Reviewer's Analyses	Applicant's Analyses
PopPK model-derived	78.5 vs. 111.6	13%↓	12%↓*
JZP258-101	62.3 vs. 120.2	22%↓	20%↓**

** Estimate based on applicant's response to IR received 05/21/2020; **Estimated by reviewer based on the estimates from applicant's response*.

Reviewer's note:

Though the applicant's popPK model was able to reasonably characterize the observed PK data and can be considered acceptable, the popPK-based simulated Cmax was either under/over-estimated for typical individuals within a bodyweight range of 45 – 105 kg. Overall, the reviewer's analyses indicated that the reduction in Cmax following first dose of Xyrem under the worst-case scenario translates to a potential loss of efficacy in TCAT by 30-40% and ESS scores by 10-20%, and these estimates in reasonable agreement with the applicant's estimates: TCAT by 20-40% and ESS scores by 10-20%.

Conclusion

It is worth noting that the patients in pivotal phase 3 study 15-006 were instructed to take the first dose of JZP-258 at least 2 hours after eating, which is also consistent with the recommendations included in USPI for Xyrem. The approved dosage regimens for JZP-258 mirror the recommendations for Xyrem USPI for both adult and pediatric populations. As noted previously, Cmax following first dose of JZP-258 failed to meet criteria compared to that of Xyrem (mean reduction of 26%). The worst-case scenario showed that there is a potential loss of efficacy in TCAT and ESS score, and in light of these considerations, the clinical pharmacology review team recommends that the first dose of JZP-258 should be administered at least 2 hours after eating in all patients (both those who are initiating JZP-258 as well as patients who are switching to JZP-258). Even the patients who switch from Xyrem to Xywav at the same dose and regimen as

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Xyrem, and subsequently titrated based on efficacy and tolerability should follow the instructions to take JZP-258 at least 2 hours after meals because the potential for loss of efficacy still remains if they take it without regard to food.

List of Analysis Codes and Output Files

Filename	Description	Link to PM Review Shared Drive
ERIMSET.csv	Simulation dataset for popPK analyses	\\cdsnas\Pharmacometrics\Reviews\Ongoing PM Reviews\Xywav_NDA212690_GG\Exposure Response\Reviewers Analyses
TCAT_E-R_BothStudies.R ESS_E-R_Study15.R	E-R analyses for both TCAT and ESS scores and plotting in R	

Reference ID: 4634681

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/s/

GOPICHAND GOTTIPATI
07/01/2020 03:07:28 PM

VENKATESH A BHATTARAM
07/01/2020 03:10:27 PM

SREEDHARAN N SABARINATH
07/01/2020 03:16:57 PM

MEHUL U MEHTA
07/01/2020 03:23:30 PM