CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
Addendum to Clinical Pharmacology Review

NDA or BLA Number	214755
Link to EDR	\\CDSESUB1\evsprod\NDA214755\0001
Submission Date(s)	15-Dec-2020
Submission Type	505(b)(2) (Standard Review)
Brand Name	Lumryz (FT218)
Generic Name	Sodium oxybate
Formulation and Strength	Extended-release powder for oral suspension, 4.5, 6, 7.5, and 9 g
Route of Administration	Oral Administration
Proposed Indication	Cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Applicant	Avadel Pharmaceuticals
Associated IND	IND 126321
Reviewers	Dawei Li, Ph.D.
Team Leader	Bilal AbuAsal, Ph.D.
OCP Division	Division of Neuropsychiatric Pharmacology
Division Director	Mehul Mehta, Ph.D.

On October 14, 2021, the Office of Clinical Pharmacology, Division of Neuropsychiatric Pharmacology (or the review team) finalized its clinical pharmacology review (REV-CLINPHARM-21 (Primary Review)) of Avadel's 505(b)(2) application (new drug application (NDA) 214755) for Lumryz (sodium oxybate) for extended-release oral suspension (Lumryz), which included recommendations regarding the language to be included in certain sections of the proposed product labeling. After finalizing that review, the review team for this application had further discussions about the proposed labeling for this pending application. This addendum is intended to modify the review team's recommendations for the language in section 5.1 of the Lumryz labeling provided in the October 14, 2021, clinical pharmacology review. This addendum also describes the review team's conclusion regarding whether a section 7.2 for the Lumryz prescribing information is needed. This addendum also describes another drug-drug interaction study that Avadel conducted involving concomitant administration of Lumryz and divalproex sodium not previously described in the October 14, 2021, clinical pharmacology review.

As described in the October 14, 2021, review, Avadel conducted a drug-drug interaction study (Study PFKT218-1901 or Study 1901) to evaluate the potential interaction between Lumryz and divalproex sodium. Although FDA did not require Avadel to conduct a drug-drug interaction study prior to submission of its application,[1] Avadel conducted this drug-drug interaction study

[1] FDA acknowledged in pre-NDA correspondence that the study results would inform FDA's review of the proposed prescribing information. Specifically, FDA noted that if no significant drug-drug interaction is identified in Avadel's drug-drug interaction study and no dose adjustment is needed, it may be acceptable to describe the study

(Study 1901) to assess both pharmacokinetics and safety endpoints associated with co-administration of Lumryz and divalproex sodium ER. Although Avadel's drug-drug interaction study did not include pharmacodynamic endpoints, the review team considers the design of this study adequate to assess pharmacokinetics and safety information associated with co-administration of Lumryz and divalproex sodium ER. As noted in the October 14, 2021, review, the findings from Study 1901 reflect no significant pharmacokinetic interaction between Lumryz and divalproex sodium ER. Therefore, the review team did not recommend, in the review dated October 14, 2021, that the Lumryz prescribing information include a specific dose adjustment when Lumryz is co-administered with divalproex sodium.[2] However, the review team did note that since divalproex sodium is a sedative anti-epileptic drug that may lead to CNS depression, the potential of a pharmacodynamic interaction between Lumryz (also a CNS depressant) and divalproex sodium cannot be ruled out. Additionally, at that time, the review team recommended adding divalproex sodium as an example of sedating anti-epileptic drugs in section 5.1 to warn that the concurrent use of Lumryz with sedating anti-epileptic drugs (e.g., phenytoin, divalproex sodium, levetiracetam), may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

The review team affirms its conclusions described in the October 14, 2021, review that there is no significant pharmacokinetic interaction between Lumryz and divalproex sodium and therefore no specific dose adjustment recommendation is needed (based on the PK results) when Lumryz and divalproex sodium are concomitantly administered. The review team also affirms that a pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out.[3] The review team, however, has changed its position on adding examples of sedating anti-epileptic drugs – specifically, phenytoin, divalproex sodium, levetiracetam – in section 5.1 of the Lumryz prescribing information. After further consideration of the prescribing information for Lumryz, the review team notes that section 5.1 is intended to describe the general risks associated with use of CNS depressants (alone or in combination with other CNS depressants), is based on long-standing knowledge about the general risks associated with use of CNS depressants, and is intended to inform healthcare prescribers of the general risks associated with CNS depressants. Therefore, identifying specific anti-epileptic drugs (e.g., phenytoin, divalproex sodium, levetiracetam), is not necessary, and the specific examples should not be included in section 5.1 of the prescribing information for Lumryz.

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results in Section 12 of the prescribing information, but omit dose reduction recommendations (i.e., in Section 2 or 7). See, for example, FDA's written responses to Avadel's questions dated December 4, 2019 (IND 126321).

[2] It is noted that the October 14, 2021, OCP review states "[t]he PD interaction was not evaluated in this study and hence, no specific dose adjustment recommendation can be made." The statement in the review that no specific dose adjustment recommendation can be made for Lumryz incorrectly ties the lack of a dose adjustment to the lack of PD data. The lack of a dose adjustment recommendation should be understood in the context of the study 1901 results, which showed no significant PK interaction, but did not rule out the possibility of a PD interaction because of the general risks associated with CNS depressant use.

[3] Although a PD interaction cannot be ruled out, we conclude that the Lumryz prescribing information is sufficient given the PK results from Study 1901 and the general warning in section 5.1 about using Lumryz with other CNS depressants.

On September 23, 2021, proposed draft labeling language for section 7.2 of the prescribing information was provided by the review team to Avadel. The text of the proposed section 7.2 read as follows:

(b) (4)

In transmitting this proposed labeling language to Avadel, the review team included the following note:

> Note to applicant: We agree that the pK increases are not expected to be clinically significant; however, there is a PD interaction with divalproex sodium and sodium oxybate. Therefore, we have included this subsection.

As described above, a PD interaction between Lumryz and divalproex sodium cannot be ruled out given that both are CNS depressants. This drafting comment was not intended to suggest that there was an established PD interaction between Lumryz and divalproex sodium based on specific study data nor that there existed a significant pharmacokinetic interaction between Lumryz and divalproex sodium. Instead, this drafting comment was intended to underscore the general risks associated with use of CNS depressants (alone or in combination with other CNS depressants) and the potential PD interaction between Lumryz and divalproex sodium, and to acknowledge the finding from Study 1901 that no significant pharmacokinetic interaction between Lumryz and divalproex sodium ER was established. It is the review team's position that the description of the general risks associated with use of CNS depressants in section 5.1 of the prescribing information is sufficient to inform healthcare prescribers of the risks associated with using Lumryz with other CNS depressants, including divalproex sodium. Additionally, we note that the language in proposed section 7.2 stating that (b) (4) was provided to Avadel at an interim point in the review prior to the review team's conclusion that there is no significant pharmacokinetic interaction between Lumryz and divalproex sodium even if a PD interaction cannot be ruled out. Now that the review team has thoroughly analyzed the information from Study 1901, we conclude that a separate section 7.2 would only duplicate the general information otherwise included in section 5.1 (based on the general risks associated with CNS depressants) and is not necessary to adequately inform prescribers of the general risk associated with CNS depressants.

In addition to Study 1901, Avadel conducted another drug-drug interaction study involving concomitant administration of Lumryz and divalproex sodium ER (Study PKFT218-1702 or Study 1702). Although the findings for study 1702 were consistent with the findings from Study 1901 (Co-administration of a single 6 g dose of LUMRYZ with divalproex sodium ER at steady state resulted in an approximate 18% increase in AUC, while Cmax was comparable), Study 1702 was conducted by administering the study drugs in the morning, two hours after completion

of breakfast. In contrast, Study 1901 administered the study drugs in the evening, two hours after dinner. The review team notes that evening dosing is more consistent with the dosage and administration recommendations for Lumryz (i.e., night-time dosing) and, thus, the relevant study for purposes of concluding that there is no significant pharmacokinetic interaction between Lumryz and divalproex sodium and for informing the contents of the Lumryz prescribing information is Study 1901.

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OFFICE OF CLINICAL PHARMACOLOGY

Clinical Pharmacology Review

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Link to EDR	\\CDSESUB1\evsprod\NDA214755\0001
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OCP Division	Division of Neuropsychiatric Pharmacology
Division Director	Mehul Mehta, Ph.D.

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1 Executive Summary

Avadel Pharmaceuticals is seeking approval for Lumryz (Sodium oxybate ER oral suspension) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy under the 505(b)(2) pathway using Xyrem as the reference product[1]. Avadel's rationale for the development of Lumrys was to create an oral suspension of sodium oxybate that could be dosed once at bedtime rather than by the divided dosing scheme of Xyrem®. Lumryz has been developed using controlled-release technology designed to extend and/or delay the absorption time of the drug.

The proposed Lumryz starting dosage is 4.5 grams (g) per night administered orally, then titrate to effect in increments of 1.5 g per night at weekly intervals to effective dosage range of 6 g to 9 g per night.

The clinical efficacy and safety of Lumryz for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy has been established based on results from phase 3 double-blind, randomized, placebo-controlled study (CLFT218-1501). The co-primary endpoints for evaluating EDS in both NT1 and NT2 narcolepsy subjects were the mean sleep latency on the Maintenance of Wakefulness (MWT) and the CGI-Improvement (CGI-I). The primary endpoint for evaluating cataplexy was the number of cataplexy attacks (NCA, NT1 subjects only). Per the applicant conducted analysis, once-nightly Lumryz treatment at all tested dose (6 g, 7.5 g and 9 g) demonstrated statistically significant improvement compared to placebo on the three co-primary endpoints.

The application package also included the following key clinical pharmacology studies:

- Study PKFT218-1801 is a relative bioavailability pharmacokinetic study at the dose of 6 g to bridge Lumryz to the listed drug (Xyrem, NDA 21196). While the shape of the PK profile after the daily dosing is different, results from this study showed comparable total exposure (AUC) between Lumryz and the reference product Xyrem which supported the efficacy and safety of Lumryz.
- Study PKFT218-1601 is a PK study to assess the dose proportionality of Lumryz at doses of 4.5 g, 7.5 g and 9 g
- Study PKFT218-1901 is a drug-drug interaction study to assess the effect of divalproex sodium at steady state on the PK of Lumryz. Results from this study showed no significant PK interaction with divalproex sodium. However, since divalproex sodium is a sedative anti-epileptic drug that may lead to CNS depression, the PD interaction can't be ruled out. The PD interaction was not evaluated in this study and hence, no specific dose adjustment recommendation can be made. Accordingly, the review team recommends adding divalproex sodium as an example of sedating anti-epileptic drugs in section 5.1 to warn the risk of the concurrent use of Lumryz with divalproex sodium.
- Study PKFT218-1603 is a food effect study to assess the impact of high-fat food on the PK of Lumryz. Results from this study showed that food decreases Cmax and delays Tmax of

[1] Xyrem USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021196s032lbl.pdf

Lumryz. Accordingly, the review team recommends that Lumryz should be taken at least 2 hours after eating, consistent with dosing recommendation in the pivotal efficacy study CLFT218

The primary focus of this review is to evaluate the adequacy of the bridging information and clinical pharmacology information to support the labeling of Lumryz.

The Office of Study Integrity and Surveillance (OSIS) was consulted for analytical site inspection for study PKFT218-1801. On 09/23/2021, OSIS concluded that the data from study PKFT218-1801 are reliable.

1.1 Recommendation

The Division of Neuropsychiatric Pharmacology has reviewed the submitted application and has found it acceptable for approval of Lumryz from a clinical pharmacology standpoint.

1.2 Post-marketing Requirement

None

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

The mechanism of action of Lumryz in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Lumryz on cataplexy and excessive daytime sleepiness are mediated through GABAB actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.[1]

Absorption

Following oral administration of Lumryz, the time to peak plasma concentration (Tmax) was 1.5 hours.

Following oral administration of Lumryz, the plasma levels of GHB increased more than dose-proportionally, with Cmax increasing approximately 2-fold and AUC increasing 2.3-fold as total daily dose is doubled from 4.5 g to 9 g.

Administration of Lumryz immediately after a high-fat meal resulted in a mean reduction in Cmax and AUC of GHB by 33% and 14% respectively, and average Tmax increased from 0.5 hr to 1.5 hr.

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.[1]

Metabolism and Excretion

[1] Xyrem USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021196s032lbl.pdf

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.[1]

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 0.5 to 1 hour.[1]

Specific Population

Lumryz should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of Lumryz cannot be made with the available dosage strengths. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz if the appropriate dosage strength is available (see section 3.2.4).

No pharmacokinetic study in patients with renal impairment has been conducted.

Drug-Drug Interaction

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with recommended doses.[1]

Co-administration of a single dose of Lumryz (6 g) with divalproex sodium ER at steady state resulted in comparable systemic exposure to GHB as shown by plasma Cmax and AUC values. A single dose of Lumryz (6 g) did not appear to affect the pharmacokinetics of divalproex sodium. However, since divalproex sodium is a sedative anti-epileptic drug that may lead to CNS depression, the potential of pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out (see section 3.2.5). The review team recommends adding divalproex sodium as an example of sedating anti-epileptic drugs in section 5.1.

2.2 Dosing and Therapeutic Individualization

General dosing

The proposed Lumryz starting dosage is 4.5 grams (g) per night administered orally, then titrate to effect in increments of 1.5 g per night at weekly intervals to effective dosage range of 6 g to 9 g per night orally.

Therapeutic individualization

[redacted] (b) (4) The review team recommends that patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz. No therapeutic individualization

[1] Xyrem USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021196s032lbl.pdf

for other intrinsic or extrinsic factors is recommended (e.g. renal impairment).

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology review team accepts the labeling concepts proposed by the applicant, except for their proposal in the following sections.

Section 2.2

(b) (4). The review team recommends that Lumryz should be taken at least 2 hours after eating, consistent with dosing recommendation in the pivotal efficacy study CLFT218-. Please refer section 3.2.5 for additional details.

Section 5.1 and 12.3

(b) (4)

As the pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out, the review team recommends revising the DDI study description in section 12.3, deleting (b) (4) The review team recommended combining divalproex sodium with phenytoin, divalproex sodium, levetiracetam as examples of sedating anti-epileptic drugs in section 5.1. In this section there is warning language about the risk of concomitant use of this class of medications with Lumryz. Please refer section 3.2.5 for additional details.

Section 4 and 8.6

As the dose adjustment for patients with hepatic impairment cannot be made with the available dosage strengths. (b) (4) The review team recommends that Lumryz should not be initiated in patients with hepatic impairment. However, patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz if the appropriate dose strength is available.

3 Comprehensive Clinical Pharmacology Review

3.1 General Pharmacological and Pharmacokinetic Characteristics

Please refer to the general clinical pharmacology information included in the USPI for the listed drug (Xyrem, NDA 21196) for additional details on distribution, metabolism and excretion of GHB.

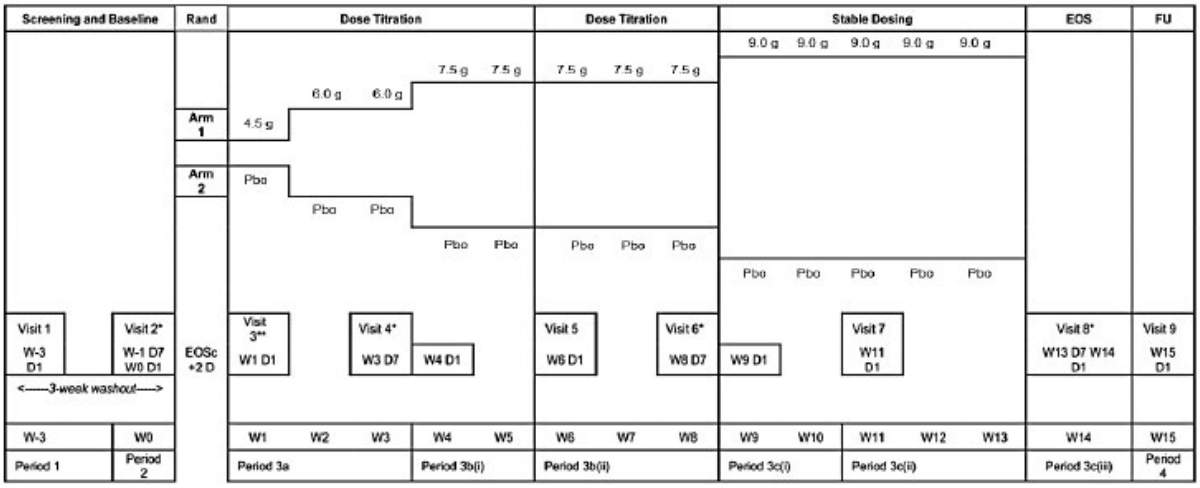
3.2 Clinical Pharmacology Review Questions

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

The evidence of effectiveness of Lumryz is primarily based on one phase 3 pivotal, multicenter,

randomized, double-blind (DB), placebo-controlled, study (CLFT218-1501). Two populations of narcoleptic subjects (NT1 and NT2) were studied in a single parallel group design. Randomization methods stratified eligible subjects by narcolepsy type in a 1:1 ratio to treatment with either Lumryz or placebo. Subjects were randomized to achieve ≥ 70 completers per arm with EDS and ≥ 50 subjects per arm with both EDS and cataplexy. The study schematic is presented in Figure 1.

Figure 1. CLFT218-1501 Study Schematic



Abbreviations: D = day; EOS = end of study; EOSc = End of Screening; FU = Follow-up; Pbo = placebo; Rand = randomization; W = week; W/O = Washout
*Study visits where baseline assessment or full efficacy assessment were done extend into the following day and are thus indicated
**Up to 6 days were allowed between randomization (which occurred up to 2 days after the end of the screening period) and dosing to allow shipment of study drug to site. (Duration between end of screening period and dosing was to be ≤ seven days).

Source: CLFT218-1501 CSR Figure 2 on page19;

Three therapeutic doses were tested under forced up-titration (6.0, 7.5, and 9.0 g). The study design allowed for forced dose increments at fixed times from 4.5 g/night followed by 1.5 g/night increments until the final 9.0 g dose was reached. Subjects remained on the 4.5 g dose for 1 week, the 6.0 g dose for 2 weeks, the 7.5 g dose for 5 weeks, and the 9.0 g dose for 5 weeks, with safety and efficacy evaluations conducted over a 12-week period (total of 13 weeks on study drug).

The co-primary endpoints for evaluating EDS in both NT1 and NT2 narcolepsy subjects were the mean sleep latency on the MWT and the CGI for sleepiness. The primary endpoint for evaluating cataplexy was the NCA (NT1 subjects only).

Per the applicant conducted analysis in a hierarchical manner, study CLFT218-1501 met the pre-specified statistical criteria for 3 co-primary endpoint (summarized in Table 1-3 below) and six out of seven secondary endpoints (No significant differences in the Number of Hypnogogic Hallucinations were observed after treatment with any dose of Lumryz when compared to placebo). Additionally, the same patients were up-titrated from 4.5 g to 9.0 g, dose-response analysis indicated that higher efficacy was associated with increased doses in the same patients. Please refer to the clinical review and statistical review for further details.

Table 1. MWT Mean Sleep Latency Change from Baseline (mITT Population)

Visit Treatment Group	N	Observed mean (SD)	LS mean (SE) of change from baseline	Difference from placebo		
				LS mean difference	95% CI	P value[1]
Baseline						
FT218	97	5.0 (3.15)	—	—	—	—
Placebo	93	4.7 (2.58)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	87	8.1 (8.38)	8.1 (0.75)	4.98	2.90, 7.05	< 0.001
Placebo	88	3.1 (5.15)	3.1 (0.74)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	76	9.6 (9.24)	9.6 (0.86)	6.21	3.84, 8.58	< 0.001
Placebo	78	3.0 (5.63)	3.3 (0.84)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	68	10.5 (8.89)	10.8 (0.96)	6.13	3.52, 8.75	< 0.001
Placebo	78	4.5 (7.40)	4.7 (0.92)	—	—	—

Table 2. Summary of CGI of Sleepiness over Time (mITT Population)

Visit Treatment Group	N	Observed mean (SD)	Response rate (% much improved or very much improved)	Odds ratio	95% CI	P value[1]
CGI-Severity at baseline[2]						
FT218	96	5.1 (1.12)	—	—	—	—
Placebo	92	5.1 (1.15)	—	—	—	—
CGI-Improvement at Visit 4 (Week 3)						
6.0 g FT218	87	2.7 (0.89)	40.1	10.29	3.93, 26.92	< 0.001
Placebo	87	3.6 (0.87)	6.1	—	—	—
CGI-Improvement at Visit 6 (Week 8)						
7.5 g FT218	75	2.4 (0.90)	62.6	5.67	2.82, 11.40	< 0.001
Placebo	81	3.3 (1.10)	22.8	—	—	—
CGI-Improvement at Visit 8 (Week 13)						
9.0 g FT218	69	2.1 (0.89)	72.0	5.56	2.76, 11.23	< 0.001
Placebo	79	3.1 (1.07)	31.6	—	—	—

Table 3. Summary of CGI of Sleepiness over Time (mITT Population)

Visit Treatment group	N	Observed mean (SD)	N	LS mean (SE) of change from baseline	Difference from placebo		
					LS mean difference	95% CI	P value[1]
Baseline							
FT218	73	18.9 (8.70)	—	—	—	—	—
Placebo	72	19.8 (8.87)	—	—	—	—	—
Change to Visit 4 (Week 3)							
6.0 g FT218	73	−7.1 (6.68)	73	−7.4 (0.79)	−4.83	−7.04, −2.62	< 0.001
Placebo	72	−2.7 (7.40)	72	−2.6 (0.79)	—	—	—
Change to Visit 6 (Week 8)							
7.5 g FT218	62	−10.4 (8.36)	66	−10.0 (0.89)	−6.27	−8.74, −3.81	< 0.001
Placebo	66	−4.1 (8.40)	69	−3.7 (0.88)	—	—	—
Change to Visit 8 (Week 13)							
9.0 g FT218	54	−11.5 (9.22)	55	−11.5 (0.96)	−6.65	−9.32, −3.98	< 0.001
Placebo	62	−4.9 (8.67)	62	−4.9 (0.95)	—	—	—

Source: CLFT218-1501 CSR Figure 18, 19 and 20 on pages 70, 71 and 72;

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

In study CLFT218-1501, the efficacy and safety of the following dosing regimen were evaluated in narcoleptic subjects (NT1 and NT2): starting dose of 4.5 g per night for 1 week, followed by increments of 1.5 g per night to 6 g per night for 2 weeks, then increased to 7.5 g dose per night for 5 weeks, and the 9.0 g dose per night for 5 weeks.

The proposed dosing regimen is similar to those evaluated in the pivotal phase 3 study where they demonstrated efficacy by meeting the pre-specified statistical criteria 3 co-primary endpoints (summarized in Table 1-3, section 3.2.1).

Lumryz was generally safe and tolerated for all doses evaluated in study CLFT218-1501. The most common AEs and adverse reactions were nausea, headache, vomiting, dizziness, enuresis, and decreased appetite. In general, these findings are consistent with the known safety profile of sodium oxybate. Please refer to the clinical safety review by Dr. Ranjit Mani for further details.

It should also be noted that the total daily exposures for the proposed doses for Lumryz are similar to exposures obtained from Xyrem. Study PKFT218-1801 suggested that the overall (AUC0-t and AUC0-inf) and peak (Cmax) exposures of GHB following treatment with 6.0 g Lumryz as a single dose were comparable to those after two doses of US Xyrem 3.0 g four hours apart with the 90% CI of geometric mean ratios for AUCs and Cmax were within the limits of 80%-125%. Please refer to section 3.2.3 for more details. In addition, results from study PKFT218-1601 showed that following oral administration of Lumryz, the plasma levels of GHB increased more than dose-proportional manner. Cmax increasing approximately 2-fold and AUC increasing 2.3-fold as total daily dose is doubled from 4.5 g to 9 g. With Xyrem (immediate

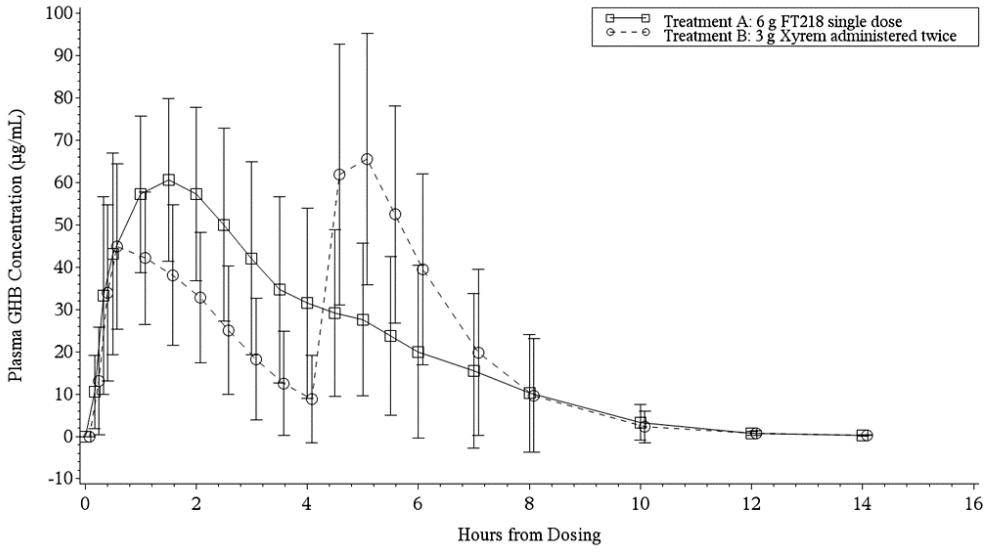
release formulation of GHB), the plasma levels of GHB also increased more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g (2.25g administered twice 4h apart) to 9 g (4.5g administered twice 4h apart). Based on this information the exposures of GHB following oral administration of Lumryz at 6 g, 7.5 g and 9 g are expected to be comparable (for daily doses equal or lower than 6 gm) or lower (for higher doses) when compared to corresponding Xyrem dose levels (administered twice 4h apart). Therefore, the safety of Lumryz at 6 g, 7.5 g and 9 g can be covered by the safety findings of Xyrem at the same doses.

Overall, the proposed dosing regimen is supported by the efficacy and safety results in study CLFT218-1501 and clinical pharmacology studies (PKFT218-1801 and PKFT218-1601).

3.2.3 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference product?

A Phase 1 comparative pharmacokinetic study (PKFT218-1801) was conducted to evaluate the relative bioavailability of Lumryz compared with the reference listed product (US Xyrem). Results from this relative bioavailability study was used to bridge the safety of Lumryz to the reference listed product (US Xyrem). In study PKFT218-1801, healthy adult volunteers received a single oral dose of 6.0 g of Lumryz (taken two hours after an evening meal) and two oral doses of 3.0 g of US Xyrem (taken two hours after an evening meal and again four hours later). Plasma GHB concentrations vs. time profiles for both treatments are illustrated in Figure 2. Lumryz showed different shape of GHB concentrations vs. time profile as compared to Xyrem. Therefore, the sponsor conducted a phase 3 study (CLFT218-1501) as confirmatory efficacy study.

Figure 2. Mean (SD) Plasma GHB Concentration vs. Time Profiles for 6.0 g FT218 and 6.0 g USXyrem, Linear Scale



Source: PKFT218-1801 CSR Figure 1 on 41;

The geometric means of AUC0-t, AUC0-inf, and Cmax following treatment with 6.0 g Lumryz as a

single dose were comparable to those following two doses of US Xyrem 3.0 g four hours apart with 90% CIs were contained within the 80% to 125% range (see Table 4). However, at higher doses (e.g., 7.5 and 9 g), the exposures of GHB following oral administration of Lumryz are expected to be lower than those after oral administration of Xyrem at the same doses (administered twice 4h apart), as Lumryz demonstrates different dose proportionality profile as compared to Xyrem (see section 3.2.2 for further details).

Table 4. Summary of Relative Bioavailability Study (PKFT218-1801)

PK parameter (unit)	Geometric LS means				Geometric mean ratio	90% CI	Intra-subject %CV
	n	Test (A)	n	Reference (B)			
AUC_{0-t} (µg•h/mL)	23	241.09	23	234.37	102.87	97.96, 108.02	9.58
AUC_{0-inf} (µg•h/mL)	23	241.83	23	235.10	102.87	97.96, 108.02	9.57
C_{max} (µg/mL)	23	62.80	23	71.09	88.34	80.48, 96.96	18.36
C_{8h} (µg/mL)	20	2.2642	23	3.6720	61.66	45.82, 82.98	58.23

Source: PKFT218-1801 CSR Table 12 on 45;

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

According to the USPI of Xyrem, AUC values were double in patients with hepatic impairment compared to healthy adults, hence starting dosage in patients with hepatic impairment is one-half of the original dosage per night due to the increased exposure in patients with hepatic impairment. However, appropriate dosage adjustments for initiation of Lumryz in patients with hepatic impairment cannot be made with the available dosage strengths. (b) (4) . The review team recommended that Lumryz should not be initiated in patients with hepatic impairment. However, patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz if the appropriate dose strength is available. Dose proportionality data from study PKFT218-1601 suggested Lumryz exhibited different dose proportionality profile from that of Xyrem, the exposure of GHB following oral administration of Lumryz at 9 g are expected to be slightly lower than the corresponding equivalent daily dose of Xyrem (4.5 g X2) (section 3.2.2). However, patients with hepatic impairment should not be exposed to 9 g of Lumryz because those patients are expected to have doubled exposure compared to patients with normal hepatic function. 4.5 g dose of Lumryz in patients with hepatic impairment should yield similar exposure to the highest approved dose (9 g) for patients with normal hepatic function. 4.5 g dose of Lumryz is expected to give the exposure comparable to that of 2.25 gX2 dose of the reference product (Xyrem, NDA 21196). It should be noted that the exposure of the 9 gm Lumryz dose was shown to be effective based on results from study CLFT218-1501.

3.2.5 Are there clinically relevant food-drug or drug-drug interactions

Food-drug interactions

Food-effect study conducted in healthy subjects indicated that high fat food reduced the Cmax and AUC of GHB by 33% and 14%, respectively (Study PKFT218-1603). Tmax was delayed (approximately 1 hour's delay) in the presence of high fat food. As the geometric means ratio for Cmax was 66.74%, with the associated 90% CI of 58.2%-76.5%, which was not contained in the standard equivalence limits of 80.00%-125.00%. (b) (4)

The review team recommends that Lumryz should be administered at least 2 hours after taking food, which is the same recommendation as the listed drug (Xyrem, NDA 21196). Additionally, this dose instruction was based on the dosing instructions for the pivotal efficacy study (CLFT218-1501), in which study subjects were instructed to take their nightly dose at least 2 hours after eating.

Drug-drug interaction

In a single-center, open-label, sequential drug-drug interaction study (PKFT218-1901), the pharmacokinetics (PK) of a single 6-g dose of Lumryz with or without 1250 mg/day divalproex sodium ER at steady-state were evaluated in 24 healthy male subjects. All enrolled subjects received three sequential treatments: 6 g Lumryz (Day 1), daily administration of 1250 mg/day divalproex sodium ER to reach steady-state (Day 2 to Day 11), and co-administration of 1250 mg divalproex sodium ER and 6 g Lumryz, with divalproex sodium ER administered first (Day 12). The PK parameters for GHB were calculated for Lumryz treatments without and with divalproex sodium ER on Day 1 and Day 12, respectively, with blood samples collected pre-dose and 10, 20, and 30 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, and 14 hours post-dose.

The PK parameters for GHB were calculated for Lumryz treatments without and with divalproex sodium ER in the evening of Day 1 and Day 12, respectively (see Table 5). The Cmax, AUC0-inf, and AUC0-t for GHB following co-administration of 6 g Lumryz and 1250 mg divalproex sodium ER (Test [T]) were compared to administration of 6 g Lumryz (Reference [R]). As shown in Table 6, the 90% CIs of the ratio of the mean of Cmax, AUC0-inf, and AUC0-t were within the accepted 80% to 125% equivalence range with T/R [90% CI]: 98.46 [91.58-105.85], T/R [90% CI]: 117.52 [111.99-123.32], and T/R [90% CI]: 117.42 [112.09-123.01], respectively. Mean tmax was delayed by approximately 0.4 hour.

Table 5: Summary of GHB Plasma Pharmacokinetic Parameters

Parameter (unit)	Statistic	Day 1	Day 12
C_{max} (µg/mL)	n	24	23
	Geometric mean	77.2	75.6
	Mean	79.8	77.8
	Min - Max	36.9 - 128	50.8 - 119
t_{max} (h)	n	24	23
	Median	1.26	2.00
	Mean	1.33	1.74
	Min - Max	0.33 - 3.00	0.33 - 3.50
C_{8h} (µg/mL)	n	24	23
	Geometric mean	2.25	5.45
	Mean	4.01	10.6
	Min - Max	0.208 - 16.7	0.296 - 41.6
AUC_{0-8h} (h·µg/mL)	n	24	23
	Geometric mean	285	331
	Mean	304	356
	Min - Max	104 - 581	105 - 680
AUC_{0-t} (h·µg/mL)	n	24	23
	Geometric mean	288	340
	Mean	307	368
	Min - Max	104 - 595	105 - 749
AUC_{0-inf} (h·µg/mL)	n	23	22
	Geometric mean	293	347
	Mean	312	375
	Min - Max	104 - 595	107 - 749
$t_{1/2}$ (h)	n	23	22
	Geometric mean	0.591	0.699
	Mean	0.608	0.716
	Min - Max	0.409 - 1.11	0.435 - 1.23

GHB=gamma-hydroxybutyric acid; Max=maximum; Min=minimum; n=number of subjects in this category

Source: PKFT218-1901 CSR Table 8 on 59;

Table 6. Drug-Drug Interaction Statistical Analysis of GHB Pharmacokinetic Parameters

Treatment Comparison (Test vs. Reference)	PK Parameter	Geometric LS means Test	n	Reference	n	Ratio Test/Reference 90% CI Estimate %	Lower %	Upper %	ISCV%
DVP+FT218 vs. FT218	C_{max} (µg/mL)	75.6	23	76.8	23	98.46	91.58	105.85	14.4
	AUC_{0-inf} (h·µg/mL)	347	22	295	22	117.52	111.99	123.32	9.3
	AUC_{0-t} (h·µg/mL)	340	23	289	23	117.42	112.09	123.01	9.2

Source: PKFT218-1901 CSR Table S3 on 12;

Based on the PK results from study PKFT218-1901, the review team concluded that the impact of divalproex sodium at steady state on the pharmacokinetics of Lumryz was not significant. However, the pharmacodynamic interactions between Lumryz and divalproex sodium were not evaluated in this study, the pharmacodynamic based interactions cannot be ruled out. According to clinical experience, co-administration of sodium oxybate and sedating anti-epileptic drugs may increase the risk of certain adverse reactions. Therefore, the review team recommends adding divalproex sodium as an example of sedating anti-epileptic drugs in section 5.1 to warn that the concurrent use of Lumryz with sedating anti-epileptic drugs (e.g., phenytoin, divalproex sodium, levetiracetam), may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of the CNS depressants (including sedating anti-epileptic drugs) in combination with Lumryz is required, dose reduction or discontinuation of one or more CNS depressants should be considered. Please refer to the clinical review for further details.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

A validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) method with GHB-D6 as internal standard was employed for determining the concentrations of gamma-hydroxybutyric acid (GHB) in human plasma. The sample analysis was conducted in accordance with the FDA Guidance for the Industry, Bioanalytical Method Validation. Summary of bioanalytical methods validation is provided in Table 7.

Table 7. Summary of the GHB Assay Analytical Method Validation in Human Plasma

Validation Parameters	**Results:**
Lower Limit of Quantitation (LLOQ)	0.200 ug/mL
Calibration Concentrations (ug/mL)	0.200; 0.600; 2.00; 10.0; 25.0; 75.0; 120; 150
QC concentrations (ug/mL)	0.200; 0.600; 75.0; 120

Inter-Run Accuracy and Precision	Biases: -3.1 to 10.8%; CV: 3.6 to 6.8%
Intra-Run Accuracy and Precision	Biases: -7.8 to 19.1%; CV: 1.0 to 4.6%
Stability Period at Automatic Sampler Temperature	Stable for 311 hours 37 minutes at + 4°C
Bench Top Stability	Stable for 2 hours at room temperature in plasma
3 Freeze and Thaw Stability	Stable after 3 cycles freeze (at -80°C) and thaw (room temperature) cycles
Short-Term Stability of Analyte in Matrix	Stable 4 hours at room temperature (after a freezing period at -80°C)
Long-term storage stability in Matrix	Stable 44 days at -80°C

Source: PKH/MOA/294 method validation report

The validated assay performance was reviewed individually for the key clinical pharmacology studies. 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.

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