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APPLICATION NUMBER:

214755Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**214755 (055)**
Sponsor:	**Avadel**
Product:	**Lumryz***
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Amendment of New Drug Application**
Correspondence Date:	**3/1/23**
Date Received By Reviewer:	**3/1/23**
Date Review Completed:	**4/28/23**
Reviewer:	**Ranjit B. Mani, M.D.**

*Lumryz is the proprietary name for this product. The original name for this product is Sodium Oxybate Extended-Release for Oral Suspension (FT218).

1. Background

In this amendment of New Drug Application (NDA) 214755, the applicant has requested the final approval of Sodium Oxybate Extended-Release for Oral Suspension (FT218) for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy.

This application was originally submitted on December 15, 2020, and was granted tentative approval by the Agency in a letter dated July 18, 2022; the application was submitted pursuant to Section 505(b)(2) of the Food, Drug, and Cosmetic (FD&C) Act, relying on Xyrem as the listed drug. Please see Agency reviews of the application, and the tentative approval letter dated July 18, 2022, for full details; the application was only eligible for a tentative approval at that time because the 45-day period described in section 505(c)(3)(C) of the FD&C Act had not yet expired.

Xyrem (sodium oxybate oral solution [500 mg/mL]) is currently approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. Xyrem was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 021196. A supplemental NDA (an efficacy supplement; S-005) proposing an expansion of the originally approved indication was approved on November 18, 2005; the approved expanded indication was as follows: "*The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy*." FDA initially approved Xyrem (NDA 021196) under the restricted distribution provisions of 21 CFR 314 Subpart H, and Xyrem was approved with the Xyrem Risk Management Program to assure safe use of the product (also referred to at the time as the "Xyrem Success Program"). A Risk Evaluation and Mitigation Strategy (REMS) for Xyrem was then approved by FDA on February 27, 2015. Most recently, the Agency approved a supplement that expanded the approved use of Xyrem to the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7

years of age and older on October 26, 2018. Xyrem has been designated as a Schedule III controlled substance under the Federal Controlled Substances Act.

Another oxybate product, Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution) was approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy (i.e., the same indication as Xyrem) on July 21, 2020, under NDA 212690. Xywav has been approved under a REMS that is common to both that drug and Xyrem. Xywav, like Xyrem has been designated as a Schedule III controlled substance under the Federal Controlled Substances Act.

There are generic sodium oxybate products that are either approved or tentatively approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy: a single generic product was approved (although on the discontinued drug product list of the Orange Book), and a further three generic sodium oxybate products have received tentative approval.

Xyrem, Xywav, and the aforementioned generic formulations of sodium oxybate are all administered in two divided doses every night. However, Sodium Oxybate Extended-Release for Oral Suspension (FT218) is to be administered in a single nightly dose.

The proprietary name Lumryz has been granted for Sodium Oxybate Extended-Release for Oral Suspension (FT218).

This review is intended to serve as both a primary clinical review and as a Cross-Disciplinary Team Leader review.

2. Contents Of Submission

The main contents of this amendment as submitted on March 1, 2023, are as follows.

- Cover letter (which describes the history of this application and the contents of the submission). The letter is headed "*Request for Final Approval*."

- Patent Certification and Statement, including documentation to withdraw its prior Paragraph IV certification to the '963 patent. In its cover letter, the applicant informed the Agency that on "*November 18, 2022, the U.S. District Court for the District of Delaware ruled that the '963 patent does not claim an approved method of using the drug and ordered Jazz to request delisting of the patent from the Orange Book. On February 24, 2023, the U.S. Court of Appeals for the Federal Circuit affirmed this ruling and ordered Jazz to request delisting of the patent within 14 days (by March 10, 2023).*"

- Amended Prescribing Information and Instructions for Use ("*clean*" and "*changes tracked*" versions).

- Integrated Summary of Safety (Safety Update). This safety update is confined to the single ongoing study of Lumryz, Study CLFT218-1901, and a review of the pertinent medical literature.

Although the Risk Evaluation and Mitigation Strategy (REMS) for Lumryz is not listed immediately above, a proposed REMS for Lumryz was submitted on March 10, 2023, in response to an information request from the Agency and amended in several subsequent submissions following that.

3. Contents Of Review

The contents of this submission will be reviewed under the following headings and in the same consecutive order as below.

- List of all clinical studies conducted in support of this application.

- Safety update: Study CLFT218-1901 (RESTORE).

- Safety update: information from the medical literature.

- Review of proposed Prescribing Information and related documents.

- Risk Evaluation and Mitigation Strategy (REMS).

- Patent certification and statement.

- Reviewer's summary comments.

- Further conclusion.

- Recommendation.

4. List Of All Clinical Studies Conducted In Support Of This Application

The following is a list of all clinical studies of Sodium Oxybate Extended-Release for Oral Suspension (FT218; Lumryz) that have been conducted in support of this application.

- A main clinical efficacy and safety study (Study CLFT218-1501).

- A clinical safety study, CLFT218-1901 (ongoing).

- 10 clinical pharmacology studies: PKFT218-1301; PKFT218-1602; PKFT218-1603; PKFT218-1701; PKFT218-1801; PKFT218-1802; PKFT218-1902; PKFT218-1702; PKFT218-1901; and PKFT218-1601. Of these studies: PKFT218-1801 was considered a pivotal relative bioavailability study; and PKFT218-1901 was a drug-drug interaction study between FT218 and divalproex sodium.

Data for all studies listed above were included in the original NDA for Lumryz submitted on December 15, 2020, or in the 120-Day Safety Update. Please see my review dated July 15, 2022, for further details of those studies as described in the application. Note that the only study that had not been completed at the time of the original submission of the application, or at the time of the 120-Day Safety Update, was Study CLFT218-1901, an open-label, uncontrolled, long-term safety study; that study remains ongoing. By prior agreement with the Agency, all data for that study were included only in the 120-Day Safety Update for the application.

Thus, the only clinical study for which additional data are included in the current NDA amendment is Study CLFT218-1901. The design of that study, together with available clinical data, are summarized in the next section.

5. Safety Update: Study CLFT218-1901 (RESTORE)

5.1 Summary Of Study Design

The main features of the design of this study are summarized below, based on the most recent version of the study protocol (Version 3.0, dated May 18, 2021). This version of the study protocol was submitted to IND 126321 (for Sodium Oxybate Extended-Release for Oral Suspension [FT218]) on May 28, 2021 (under Serial #099).

The primary objective of this study was to investigate the long-term safety and tolerability of FT218. Secondary objectives of this study included evaluating the safety and tolerability (and dosing regimens) when switching from twice-nightly sodium oxybate immediate-release or mixed-salts oxybate to FT218.

This was to be an open-label uncontrolled study lasting either 24 months or until subjects could be transitioned to the commercially available product.

Subjects to be enrolled in this study were to consist of patients aged ≥ 16 years with either Type 1 or Type 2 narcolepsy and were to be in one of 3 categories:

- Group A consisting of subjects who completed Study CLFT218-1501 and had not started treatment with twice nightly sodium oxybate or twice nightly mixed salts oxybate.

- Group B, consisting of subjects who were currently receiving a stable dose of either twice-nightly sodium oxybate or twice nightly mixed salts oxybate.

- Group C, consisting of subjects who were naïve to oxybate therapy.

About 250 subjects were to be enrolled in this study.

The study was to have 3 consecutive dosing periods: Period 1, a dose-titration period; Period 2, a stable-dose period; and Period 3, a follow-up period.

The dosing regimen for each group during Study Period 1 is summarized as follows: for Groups A and C, dosing with FT218 once nightly was to begin at a dose of 4.5 g nightly, with weekly increments by 1.5 g nightly until the highest tolerated dose up to a maximum of 9.0 g nightly was reached or the dose deemed effective by the investigator was reached (titration up or down was permitted); for Group B, dosing with FT218 once nightly was to begin at a dose equivalent or closest to the total gram dose of twice-nightly sodium oxybate; that dose was then to be titrated up or down as determined by the investigator.

Safety outcome measures were to include adverse events, vital signs, safety laboratory tests, and electrocardiograms.

5.2 Summary Of Safety Data Included In 120-Day Update To The NDA

The following text in italics is copied verbatim from my review of the application. That text applies to Study CLFT218-1901, only.

The results of this ongoing study are as summarized in the 120-Day Safety Update to this NDA, submitted on April 13, 2021, and are based on an interim analysis of safety, dated February 26, 2021.

At the time the above safety analysis was conducted, 47 patients had received at least one dose of FT218 in this study; they consisted of 8 patients in Group A and 39 patients in Group B; and none of these subjects had completed the study. 3 patients in Group A and 8 patients in Group B had by then withdrawn from the study, with none of these patients discontinuing the study on account of adverse events. No patient in Group A and only 6 patients in Group B had been exposed to study medication for > 6 months.

There were no deaths, serious adverse events, or discontinuations due to adverse events seen in the study. The pattern of adverse events in that study was generally consistent with what had been observed in Study CLFT218-1501

and with other oxybate products. Vital sign and laboratory data revealed no items of significant concern.

The patient exposure to FT218 in this study was limited in regard to both the number of subjects exposed as well as duration of exposure.

5.3 Summary Of Safety Data Included In Current Submission

5.3.1 Subject Disposition

A total of 184 patients have been enrolled in Study CLFT-1901, beginning on July 7, 2020. Enrollment in this study has ceased as of June 30, 2022 (b) (4)

The safety population for this study comprised 180 patients, distributed as follows.

Group A: 15 patients.
Group B: 130 patients.
Group C: 35 patients.

5.3.2 Deaths

There were no deaths reported during this study.

5.3.3 Other Serious Adverse Events

6 subjects experienced serious adverse events. These subjects are listed below.

Subject #	Serious Adverse Event
(b) (6)	Fall (slipped in a puddle), leading to fractured ribs and pneumothorax
	Deep vein thrombosis (May-Thurner syndrome)
	Abscess (on back)
	Anxiety, followed by psychotic symptoms (delusions, auditory hallucinations, agitation)
	Pancreatitis and cholecystitis; gallstones
	Chest pain (cardiac causes ruled out)

I have read the full narratives for each of the above patients. Except in the case of Subject (b) (6), the events were unlikely to be causally linked to the study drug; however, in Subject # (b) (6), the events that occurred were entirely consistent with the previous experience with other oxybate drugs, including Lumryz.

5.3.4 Discontinuations Due To Treatment-Emergent Adverse Events

11 patients experienced 27 treatment-emergent adverse events that led to study drug discontinuation.

These included the following:

- Single reports of abdominal discomfort, abnormal dreams, anxiety, cataplexy, cluster headache, delusion, dizziness, dry mouth, epigastric pain, feeling abnormal, feeling cold, feeling jittery, hangover, headache, heart rate increased, hyperhidrosis, hypertension, nightmare, palpitations, somnolence, tremor, vomiting, and weight decreased.

- Two reports each of asthenia and nausea.

I have read the narratives for all 11 patients who experienced treatment-emergent adverse events leading to study drug discontinuation. The majority of symptoms experienced by those patients are consistent with the previous experience with oxybate drugs. None of the events described warrant further action.

5.4 Conclusions

I have concluded that the data from the ongoing Study CLFT218-1901 as well the data from the literature review described in the next section do not identify any new safety findings.

6. Safety Update: Information From The Medical Literature

The sponsor searched PubMed on January 13, 2023, for new English language articles published since the last such search was conducted on August 2, 2020. The last search was conducted to support the original NDA submission. The search terms used were "*Xyrem*" and "*sodium oxyb*ate."

8 relevant articles were identified. Several articles included reports of the administration of a marketed mixed-salt oxybate formulation.

I have read the sponsor's summaries of each paper, supplementing that by reading several of those papers in more detail.

The safety findings described in those papers are consistent with the past clinical experience with oxybate compounds.

The papers referenced by the sponsor are listed below.

Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy [published correction appears in Sleep. 2021 Jul 9;44(7):] [published correction appears in Sleep. 2021 Nov 12;44(11):]. Sleep. 2021;44(3):zsaa206.

Carbajal-Mamani S, Berry RB, Al Hourani L, Khatri A, Ryals S, Wagner MH. Knuckle cracking at night associated with sodium oxybate treatment. J Clin Sleep Med. 2021;17(5):1121–1123.

Chen, C, Jenkins, J, Zomorodi, K, Skowronski, R. Pharmacokinetics, bioavailability, and bioequivalence of lower-sodium oxybate in healthy participants in two open-label, randomized, crossover studies. Clin Transl Sci. 2021; 14: 2278– 2287.

Dauvilliers, Y., Šonka, K., Bogan, R.K. et al. Changes in Cataplexy Frequency in a Clinical Trial of Lower-Sodium Oxybate with Taper and Discontinuation of Other Anticataplectic Medications. CNS Drugs 36, 633–647 (2022).

Guiraud J, Addolorato G, Antonelli M, et al. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial. Journal of Psychopharmacology. 2022;36(10):1136-1145.

Heo, YA. Calcium, Magnesium, Potassium and Sodium Oxybates (Xywav®) in Sleep Disorders: A Profile of Its Use. CNS Drugs 36, 541–549 (2022).

Husain AM, Bujanover S, Ryan R, Scheckner B, Black J, Profant J. Incidence and duration of common, early-onset adverse events occurring during 2 randomized, placebo-controlled, phase 3 studies of sodium oxybate in participants with narcolepsy. J Clin Sleep Med. 2020;16(9):1469–1474.

Lecendreux M, Plazzi G, Dauvilliers Y, et al. Long-term safety and maintenance of efficacy of sodium oxybate in the treatment of narcolepsy with cataplexy in pediatric patients. J Clin Sleep Med. 2022;18(9):2217–2227.

7. Review Of Proposed Prescribing Information And Related Documents

I have reviewed the updated Prescribing Information proposed by the applicant together with the applicant proposals for Instructions for Use.

For the Prescribing Information proper, the sponsor has proposed changes to the following sections.

- Section 6.1 Adverse Reactions – Clinical Trials Experience.
- Section 10.2 Overdosage – Signs and Symptoms.
- Section 10.3 Overdosage – Recommended Treatment of Overdose.

The proposed changes to Section 6.1 consisted of the correction of errors.

The proposed changes to Sections 10.2 and 10.3 included acidosis as a phenomenon observed with oxybate dosage and briefly referred to its treatment. These changes followed the inclusion of similar changes in the Prescribing Information for the listed drug relied upon, Xyrem.

The proposed modifications to the Instructions for Use are intended to correct an error, and clarify text.

The Prescribing Information, Medication Guide, and Instructions for Use, as finalized at the time this review was completed, are acceptable.

8. Risk Evaluation And Mitigation Strategy (REMS)

As already noted above, a proposed REMS for Lumryz was submitted on March 10, 2023, in response to an information request from the Agency, and later amended several times; the last such amendment was submitted on April 27, 2023.

The REMS was reviewed by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medical Error Surveillance (DMAMES).

Both Divisions determined that the REMS submitted on April 27, 2023, was acceptable.

This reviewer concurs with that conclusion.

9. Patent Certification And Statement

The applicant provided a Patent Certification and Statement, including documentation to withdraw its prior Paragraph IV certification to the ’963 patent. The applicant informed the Agency that on “November 18, 2022, the U.S. District Court for the District of Delaware ruled that the ’963 patent does not claim an approved method of using the drug and ordered Jazz to request delisting of the patent from the Orange Book. On February 24, 2023, the U.S. Court of Appeals for the Federal Circuit affirmed this ruling and ordered Jazz to request delisting of the patent within 14 days (by March 10, 2023).” Jazz subsequently requested deletion of the ’963 patent from listing in the Orange Book. The ’963 patent has been removed from the Orange Book and there are no outstanding issues related to patents listed in the Orange Book that preclude final approval of the application.

10. Reviewer’s Summary Comments

In this amendment of New Drug Application (NDA) 214755, the applicant has requested the final approval of Sodium Oxybate Extended-Release for Oral Suspension (FT218) for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy.

This application was originally submitted on December 15, 2020, and was granted tentative approval by the Agency in a letter dated July 18, 2022.

The current amendment, as originally submitted, includes a cover letter, Patent Certification and Statement, amended Prescribing Information and Instructions for Use, and an Integrated Summary of Safety (Safety Update). A proposed updated Risk Evaluation and Mitigation Strategy (REMS) for Lumryz has then been submitted in response to an information request from the Agency.

The Patent Certification and Statement included in this amendment has been addressed in more detail in Section 9 of this review.

The Safety Update is confined to the single, ongoing, open-label uncontrolled study of Lumryz, Study CLFT218-1901, and a review of the pertinent medical literature. The data submitted with that update are consistent with the prior clinical experience with oxybate compounds and do not warrant further action.

The Prescribing Information, Medication Guide, and Instructions for Use, as finalized at the time this review was completed, are acceptable.

The REMS for Lumryz, as finalized at the time this review was completed, is also acceptable.

11. Further Conclusion

Finally, the Office of Orphan Products Development in consultation with Agency sleep experts and the Division of Neurology 1 ("DN1") has considered whether Xywav's unexpired orphan-drug exclusivity blocks approval of Lumryz and has determined that Lumryz's approval is not blocked, which is separately documented. In light of the above, DN1 has determined that Lumryz is approvable for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy.

12. Recommendation

I recommend that Lumryz be approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy.

Ranjit B. Mani, M.D.
Medical Reviewer

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

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RANJIT B MANI
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05/01/2023 09:01:54 AM

Review and Evaluation of Clinical Data

NDA (Serial Number)	**214755**
Applicant:	**Avadel**
Product:	**Lumryz***
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Original New Drug Application**
Correspondence Date:	**12/15/20**
Date Received By Reviewer:	**12/15/20**
Date Review Completed:	**7/14/22**
Reviewer:	**Ranjit B. Mani, M.D.**

*Lumryz is the proprietary name for this product. The original name for this product is Sodium Oxybate Extended-Release for Oral Suspension (FT218).

TABLE OF CONTENTS

Executive Summary

Recommendation

I recommend the approval of Sodium Oxybate Extended-Release for Oral Suspension (FT218), Lumryz, for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. However, the 45-day period described in section 505(c)(3)(C) of the FD&C Act has not yet expired, and this application is only eligible for a tentative approval at this time.

Proposed Indication

The proposed indication for Sodium Oxybate Extended-Release for Oral Suspension (FT218), Lumryz, is the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy.

Background To Application

Sodium Oxybate Extended-Release for Oral Suspension (FT218) drug is a proposed once-nightly formulation of sodium oxybate. This drug product is composed of both immediate-release pellets and controlled-release pellets.

There are two approved new drug applications (NDAs) for oxybate formulations for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy; these are Xyrem (sodium oxybate oral solution [500 mg/mL]) under NDA 021196 and Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution) under NDA 212690. There is one generic sodium oxybate product approved (although on the discontinued drug product list of the Orange Book) and there are also several generic sodium oxybate products tentatively approved for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. These formulations are all administered as two divided doses every night.

This application has been submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), relying on Xyrem as the listed drug.

All Clinical Studies

The clinical studies of Sodium Oxybate Extended-Release for Oral Suspension (FT218) that have been conducted in support of this application are as follows:

- A main clinical efficacy and safety study (Study CLFT218-1501).
- The clinical safety study, CLFT218-1901 (ongoing).
- 10 clinical pharmacology studies: PKFT218-1301; PKFT218-1602; PKFT218-1603; PKFT218-1701; PKFT218-1801; PKFT218-1802; PKFT218-1902;

PKFT218-1702; PKFT218-1901; and PKFT218-1601. Of these studies: PKFT218-1801 was considered a pivotal relative bioavailability study; and PKFT218-1901 was a drug-drug interaction study between FT218 and divalproex sodium.

Summary Of Main Clinical Study Supporting This Application (Study CLFT218-1501)

Study Design

The main features of Study CLFT218-1501 were as follows.

- The primary objective of that study was to demonstrate the efficacy of FT218 in doses of 6.0 g, 7.5 g, and 9.0 g nightly in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

- This was to be a randomized, double-blind, placebo-controlled, parallel-arm study.

- Two populations of patients with narcolepsy (men and women; age ≥ 16 years) were to be studied: patients with excessive daytime sleepiness and cataplexy (Type 1 narcolepsy, NT1); and patients with excessive daytime sleepiness and no cataplexy (Type 2 narcolepsy, NT2). Criteria for a diagnosis of narcolepsy with or without cataplexy were to be based on the following (and were also to meet the International Classification of Sleep Disorders-3 criteria for NT1 or NT2): the results of on overnight polysomnogram and next-day Multiple Sleep Latency test with two or more sleep-onset rapid eye movement periods and with mean sleep latency in the pathological range of < 8 minutes; and excessive daytime sleepiness for at least 3 months currently presenting with an Epworth Sleepiness Scale score > 10.

- Concomitant stimulant use was to be permitted, although not required, if the stimulant dose had been stable for at least 3 weeks at screening. Patients enrolled should have been naïve to Xyrem.

- 264 patients were to be enrolled in the study and randomized to 2 treatment arms in equal proportions (i.e., 132 patients per treatment arm): Arm 1 consisting of FT218 in a single dose of 9.0 g nightly (final dose, reached by forced dose titration beginning with a dose of 4.5 g nightly); and Arm 2 consisting of placebo administered nightly. Randomization was to be stratified according to narcolepsy type (i.e., Type 1 or Type 2). A minimum of 107 patients per treatment arm was to have Type 1 narcolepsy.

- The study was to have 9 consecutive periods be subsumed under a 3-week screening period, a 13-week treatment period, and a 1-week follow-up period.

- The primary efficacy measures were the following: Maintenance of Wakefulness score and Clinical Global Impression for excessive daytime sleepiness; and mean number of cataplexy attacks over a 2-week period. Secondary efficacy measures were to be as follows: two measures derived from polysomnography to be used as measures of disturbed nocturnal sleep; Epworth Sleepiness Scale score; number of transient nocturnal arousals (based on polysomnography); quality of sleep as measured by a visual analog scale; number of hypnagogic hallucinations as recorded in a patient-maintained diary; and the number of sleep paralysis events as recorded in a patient-maintained diary. Safety measures were to include adverse events, vital signs, safety laboratory tests, electrocardiograms, and physical examinations.

- A complex plan for sequential hypothesis testing of the primary efficacy measures was described. Hypothesis testing was to occur, comparing each dose of FT218 with placebo in descending order (i.e., FT218 9 g/day vs placebo, then FT 7.5 g/day vs placebo, and finally FT218 6 g/day vs. placebo). At each dose level, the effect of FT218 was to be compared with that of placebo first on the Maintenance of Wakefulness Test mean sleep latency score and Clinical Global Impression of Change, and then on the change from baseline to endpoint in daily cataplexy score. Each hypothesis test was to be performed at a significance level of 0.05 (two-sided). Rejection of the study hypothesis at any step was to terminate all further steps of the testing sequence. Methods of analysis were also specified for the secondary efficacy measures.

Study Results

This study was conducted according to its final protocol.

413 patients were enrolled in the study. 222 patients were randomized with at least 111 patients being assigned to each treatment group. 212 patients (107 patients in the FT218 group and 105 patients in the placebo group) received at least one dose of study medication. 148 subjects (69.8% of those randomized) completed the study: 69 patients in the FT218 treatment group and 79 patients in the placebo group.

The treatment groups were comparable on each of the 3 primary efficacy parameters at baseline. The primary efficacy analysis (conducted in the modified intent-to-treat population) indicated that FT218 demonstrated a statistically significant superiority over placebo ($p < 0.0001$) on all three primary efficacy parameters, the Maintenance of Wakefulness Test mean sleep latency, the Clinical Global Impression of Sleepiness, and the mean weekly number of

cataplexy attacks; this effect was apparent at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day). At the 9.0 g/day dose: the least squares mean difference in the change from baseline to Week 13 in mean sleep latency on the Maintenance of Wakefulness Test was 6.13 minutes; the observed mean difference in the Clinical Global Impression of Sleepiness at Week 9 was 1.0 point (with 72% of those randomized to FT218 and 31.6% of those randomized to placebo being much improved or very much improved); and the least squares mean difference in the weekly number of cataplexy attacks was -6.65.

The adverse event profile for FT218, as seen in this study was not significantly different from that of other oxybate products and did not raise any special concerns. The other safety outcomes did not reveal any data of concern.

Summary Of Long-Term Safety Study Supporting This Application (Study CLFT218-1501)

Study Design

The main features of the design of this study were as follows:

- The primary objective of this study was to investigate the long-term safety and tolerability of FT218. Secondary objectives of this study included evaluating the safety and tolerability (and dosing regimens) when switching from twice-nightly sodium oxybate immediate-release to FT218.

- This was to be an open-label uncontrolled study of 24 months duration.

- Subjects to be enrolled in this study were to consist of patients with either Type 1 or Type 2 narcolepsy and were to be in 2 groups: Group A consisting of about 100 subjects who completed Study CLFT218-1501; and Group B, consisting of about 150 subjects who were currently receiving twice-nightly sodium oxybate.

- The study was to have 3 consecutive dosing periods: Period 1, a dose-titration period lasting 1-2 months; Period 2, a stable-dose period lasting up to 24 months; and Period 3, a follow-up period lasting 1 week.

- The dosing regimen for each group during Study Period 1 is summarized as follows: for Group A, dosing with FT218 once nightly was to begin at a dose of 4.5 g nightly, with weekly increments by 1.5 g nightly until the highest tolerated dose up to a maximum of 9.0 g nightly was reached or the dose deemed effective by the investigator was reached (titration up or down was permitted); for Group B, dosing with FT218 once nightly was to begin at a dose equivalent or closest to the total gram dose of twice-nightly sodium oxybate; that dose was then to be titrated up or down as determined by the investigator.

- Safety outcome measures were to include adverse events, vital signs, safety laboratory tests, and electrocardiograms.

Study Results

The results of this ongoing study are as summarized in the 120-Day Safety Update to this NDA, submitted on April 13, 2021, and are based on an interim analysis of safety, dated February 26, 2021.

At the time the above safety analysis was conducted, 47 patients had received at least one dose of FT218 in this study; they consisted of 8 patients in Group A and 39 patients in Group B; and none of these subjects had completed the study. 3 patients in Group A and 8 patients in Group B had by then withdrawn from the study, with none of these patients discontinuing the study on account of adverse events. No patient in Group A and only 6 patients in Group B had been exposed to study medication for > 6 months.

There were no deaths, serious adverse events, or discontinuations due to adverse events seen in the study. The pattern of adverse events in that study was generally consistent with what had been observed in Study CLFT218-1501 and with other oxybate products. Vital sign and laboratory data revealed no items of significant concern.

The patient exposure to FT218 in this study was limited in regard to both the number of subjects exposed as well as duration of exposure.

Additional Clinical Studies

The additional clinical studies conducted with FT218 were the 10 clinical pharmacology studies listed above.

The safety data in these studies were generally consistent with those observed in other clinical trials of oxybate products, including other clinical trials of FT218.

Proposed Labeling And Risk Evaluation And Mitigation Strategy (REMS)

This subject is addressed later in the body of this review.

Conclusions

Substantial evidence of the efficacy of FT218 for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy is provided by the single efficacy study CLFT218-1501.

The adverse event profile of FT218 is not substantially different from that of Xyrem. The other components of the safety profile of FT218 do not reveal any data of significant clinical concern. Thus, the main safety concerns related to the

clinical use of FT218, as with other oxybate products, are the following: central nervous system depression; and abuse and misuse.

The safety profile of FT218 is acceptable in support of its approval, assuming that its clinical use will be as recommended in the Prescribing Information and as set forth under the final Risk Evaluation and Mitigation Strategy (REMS) for that product.

Although there is a difference in the shape of the pharmacokinetic profile of FT218 it has been demonstrated to have comparable total exposure to Xyrem based on the Study PKFT218-1801 results.

1. Background

In this New Drug Application (NDA), the applicant has sought the approval of Sodium Oxybate Extended-Release for Oral Suspension (FT218) for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy.

This application has been submitted together with a request for Priority Review.

This application has been submitted pursuant to section 505(b)(2) of the FD&C Act, relying on Xyrem as the listed drug.

A 120-Day Safety Update for this application was submitted on April 13, 2021.

Xyrem (sodium oxybate oral solution [500 mg/mL]) is currently approved for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. Xyrem was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 021196. A supplemental NDA (an efficacy supplement; S-005) proposing an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication was as follows: "The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy." Xyrem was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem was originally approved for marketing under a restricted distribution program. Section 505-1 of the FD&C Act establishes FDA's risk evaluation and mitigation strategy (REMS) authority. When Congress passed the FDA Amendments Act (FDAAA) in 2007, which established Section 505-1, it set forth a comprehensive statutory framework that requires a careful balance between the need to evaluate and mitigate the risks of a drug to ensure that its benefits outweigh its risks, and the potential burdens of REMS elements on patient access and the health care delivery system. For drugs previously approved under Subpart H with restricted distribution, like Xyrem, FDAAA established that they were "deemed to have in effect an approved [REMS] under Section 505-1 of the [FD&C] Act," and required the submission of a proposed REMS within 180 days for FDA's review and approval (see section 909 of FDAAA). A REMS for Xyrem was approved by FDA on February 27, 2015. Most recently, the Agency expanded the approved use of Xyrem to the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older on October 26, 2018. Xyrem has been designated as a Schedule III controlled substance under the Federal Controlled Substances Act.

Another oxybate product, Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution) was approved for the treatment of cataplexy and excessive daytime in patients 7 years of age and older with narcolepsy (i.e., the

same indication as Xyrem) on July 21, 2020, under NDA 212690. Xywav has been approved under a REMS that is common to both that drug and Xyrem. Xywav, like Xyrem has been designated as a Schedule III controlled substance under the Federal Controlled Substances Act.

There is one approved generic sodium oxybate product and there are also several tentatively approved for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy.

Xyrem, Xywav, and the aforementioned generic formulations of sodium oxybate are all administered in two divided doses every night. It is proposed that Sodium Oxybate Extended-Release for Oral Suspension (FT218) be administered in a single nightly dose.

The proprietary name Lumryz has been granted for Sodium Oxybate Extended-Release for Oral Suspension (FT218).

Sodium oxybate extended-release oral suspension was granted orphan-drug designation by this Agency for the treatment of narcolepsy on January 8, 2018.

Please also note the following:

- This review is intended to serve as both a primary clinical review and as a Cross-Disciplinary Team Leader review.

- In this review, the names "*Sodium Oxybate Extended-Release for Oral Suspension*," "*FT218*," and "*Lumryz*" have been used interchangeably. The terms "applicant" and "sponsor" are also sometimes used interchangeably in this review.

2. Contents Of Submission

This NDA submission has two main components.

- The original NDA submission of December 15, 2020, which has been provided in standard electronic Common Technical Document format. This component has five main sections, enumerated and headed as follows:

  Module 1: Administrative information and prescribing information.
  Module 2: Common Technical Document summaries.
  Module 3. Quality.
  Module 4. Nonclinical study reports.
  Module 5. Clinical study reports.

- A 120-Day Clinical Safety Update submitted on April 13, 2021, which has also been provided in standard electronic Common Technical Document

format. This component thus has two main sections, enumerated and headed as follows:

> Module 1: Administrative information and prescribing information.
> Module 5. Clinical study reports.

Since the original submission of this NDA, there have been many additional communications between the Agency and applicant.

3. Contents Of Review

The contents of this application have been reviewed under the following primary headings and in the same consecutive order as below.

- Proposed Indication for Sodium Oxybate Extended-Release for Oral Suspension (FT218).
- History of Clinical Development of Sodium Oxybate Extended-Release for Oral Suspension (FT218).
- Chemistry and Related Items.
- Overview of Clinical Studies Of Sodium Oxybate Extended-Release for Oral Suspension (FT218).
- Description of Main Clinical Efficacy Study CLFT218-1501 (REST-ON).
- 120-Day Safety Update: Study CLFT218-1901.
- Additional Clinical Studies of Sodium Oxybate Extended-Release for Oral Suspension (FT218).
- Additional Safety Data Supporting Current Application.
- Review of Proposed Prescribing Information and Related Documents.
- Summary of Statistical Review.
- Summary of Nonclinical Review.
- Summary of Clinical Pharmacology Review.
- Summary of Quality Assessment Review.
- Summary of Office of Surveillance and Epidemiology Reviews.
- Summary of Office of Prescription Drug Promotion Review.
- Summary of Patient Labeling Review.
- Summary of Controlled Substances Staff Review.
- Financial Disclosure Information.
- Site Inspection Report.
- Division of Pediatric and Maternal Health Memorandum.
- Priority Review Request.
- Patent-Related Issues.
- Overall Conclusions.
- Recommendation.

4. Proposed Indication For Sodium Oxybate Extended-Release For Oral Suspension (FT218)

The proposed indication for Sodium Oxybate Extended-Release for Oral Suspension (FT218), Lumryz, is the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy.

5. History Of Clinical Development Of Sodium Oxybate Extended-Release For Oral Suspension (FT218)

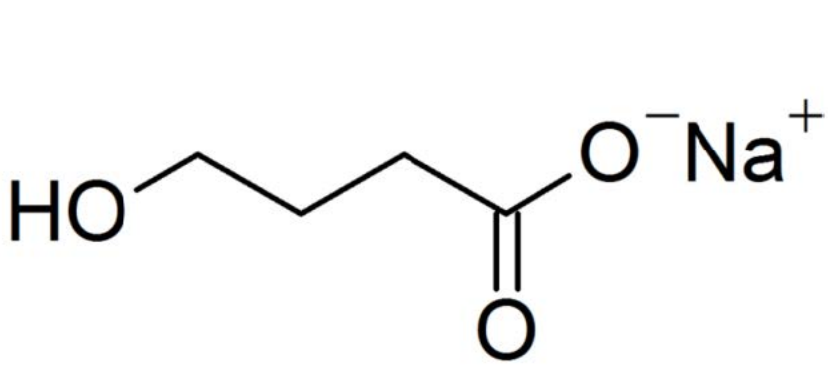
Sodium Oxybate Extended-Release for Oral Suspension (FT218) has been developed under IND 126321.

The original submission of this IND occurred on March 29, 2016, and was accompanied by a request for Special Protocol Assessment for a Phase 3 efficacy study, CLFT218-1501, which is the main clinical study included in this application. That study has since been conducted under a Special Protocol Agreement, dated October 5, 2016. The original submission of this IND was preceded by the submission of a Pre-IND Briefing Package by the current applicant on May 6, 2015, followed by a face-to-face Pre-IND meeting on June 12, 2015.

Following the initial submission of this IND application, there have been many other communications between the Agency and applicant. They have included a Pre-NDA meeting package submitted on June 5, 2020: a set of preliminary responses to the applicant's questions in that package was conveyed to the applicant on July 2, 2020, following which a planned meeting with the applicant scheduled for July 7, 2020, was canceled at the applicant's request.

6. Chemistry And Related Items

The chemical structure of the sodium oxybate drug substance is displayed below in a graphic that has been copied from this submission.



The Sodium Oxybate Extended-Release for Oral Suspension (FT218) drug product is further described below. This product is as already noted, is intended to be a once-nightly formulation; it contains sodium oxybate microparticles that are intended to be suspended in water immediately prior to oral administration.

The Sodium Oxybate Extended-Release for Oral Suspension (FT218) drug product is composed of both immediate-release pellets and controlled-release pellets. The immediate-release component represents about (b) (4)% (weight/volume) of a sodium oxybate dose and the controlled-release component represents the remaining (b) (4)% (weight/volume) of that dose. While the immediate-release component is, as expected, intended to produce an immediate clinical effect, the extended-release component is intended to provide a more prolonged effect.

The inactive ingredients in each type of pellet are listed further in the submission.

The FT218 drug product will be manufactured in the following dose units: 4.5 g, 6.0 g, 7.5 g, and 9.0 g.

Each dose of FT218 is to be packaged in an aluminum (b) (4) pack, with the contents of the package suspended in water before consumption.

Please see the Chemistry review of this application for further details.

7. Overview Of Clinical Studies Of Sodium Oxybate Extended-Release For Oral Suspension (FT218)

7.1 Outline Of Clinical Studies Of Sodium Oxybate Extended-Release for Oral Suspension (FT218)

The following clinical studies have been conducted in support of this application.

- The clinical pharmacology studies listed below:
  - PKFT218-1301.
  - PKFT218-1602.
  - PKFT218-1603.
  - PKFT218-1701.
  - PKFT218-1801.
  - PKFT218-1802.
  - PKFT218-1902.
  - PKFT218-1702.
  - PKFT218-1901.
  - PKFT218-1601.
- The clinical efficacy and safety study, CLFT218-1501.

- The clinical safety study, CLFT218-1901 (ongoing at the time of submission of this application).

The following applicant table, which I have copied from this application, provides a brief outline of the main elements of all clinical studies of Sodium Oxybate Extended-Release for Oral Suspension (FT218) that have been conducted to support this application.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report Location of Study Report
PK	PKFT218-1603	To assess the effect of food on sodium oxybate for extended release oral suspension (FT218) formulation administered at 6 g in healthy volunteers	An open-label, randomized, single dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover study Control: None	Treatment A: 6 g FT218 after a 10-hour fast Treatment B: 6 g FT218 30 minutes after the start of a standardized high-fat breakfast Powder for oral suspension, Oral	Enrolled: 16 Completed: 15	Healthy subjects	Single Dose	Completed; Full 5.3.1.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1301	To assess Sodium Oxybate in human plasma samples and to determine the corresponding pharmacokinetic parameters of three controlled release formulations of a single dosing of sodium oxybate CR taken 2 hours post-evening standardized meal, versus two divided doses of marketed reference Xyrem® taken 4 hours apart, first intake 2 hours post-evening standardized meal then 4 hours later	Single-dose, open-label, randomized Control: EU-approved Xyrem®	**Periods 1-4**: Randomized to: Test Product A: Single dose sodium oxybate CR type 1, 4.5 g Test Product B: Single dose sodium oxybate CR type 2, 4.5 g Test Product C: Single dose sodium oxybate CR type 3, 4.5 g Reference Product: Two divided doses Xyrem®, 2.25 g each **Period 5**: Randomized to receive: Test Product B: Single dose sodium oxybate CR type 2, 6 g Test Product C: Single dose sodium oxybate CR type 3, 6 g Powder for oral suspension, Oral (FT218)	Enrolled: 16 Completed: **Periods 1 -4**: Test Product A: 12 subjects Test Product B: 12 subjects Test Product C: 12 subjects Reference Product: 12 subjects **Period 5**: Test Product B: 7 subjects Test Product C: 6 subjects	Healthy subjects	FT218: Single dose Xyrem®: Two doses	Completed; Legacy 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA	PKFT218-1602	To assess the relative bioavailability and safety of sodium oxybate for extended release oral suspension (FT218) formulation (single dose of 6 g) versus the marketed reference Xyrem® (at the dose of 2 x 3 g) in healthy volunteers	A comparative, open label, randomized, 2 period, 2 sequence crossover relative bioavailability study Control: EU-approved Xyrem®	Two periods: FT218: Single dose of 6 g Xyrem®: 3 g, twice, 4 hours apart Powder for oral suspension, Oral (FT218)	Enrolled: 28 Completed: 26	Healthy subjects	FT218: Single dose Xyrem®: Two doses	Completed; Full 5.3.1.2
BE	PKFT218-1701	To demonstrate the bioequivalence of two FT218 batches (single dose of 4.5 g) in healthy volunteers	A comparative, open-label, randomized, 2-stage sequential design, 2 period, crossover study Control: None	Treatment A: 4.5 g of FT218 batch MP2 Treatment B: 4.5 g of FT218 batch MP4 Powder for oral suspension, Oral	Enrolled: 22 Completed: 21	Healthy subjects	Single Dose	Completed; Full 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA	PKFT218-1801	To demonstrate assess the relative bioavailability of FT218 when compared with the reference listed product, U.S. Xyrem® in healthy volunteers	A Comparative, Open-Label, 2-Period, Randomized, Sequential Design, Crossover Study Control: U.S.-approved Xyrem®	Treatment A: Single-dose of 6 g FT218 (powder for oral suspension) Treatment B: Single-dose of 6 g U.S. Xyrem® (oral solution) Powder for oral suspension, Oral	Enrolled: 28 Complete: 28	Healthy subjects	Single dose	Completed; Full 5.3.1.2
PK	PKFT218-1802	To assess the pharmacokinetics of two FT218 batches (single dose administered of 6 g) in healthy volunteers	An exploratory, open-label, randomized, 2 treatments, 2 periods, 2 sequences crossover study Control: None	Treatment A: Single dose of 6 g FT218 MP4 Batch A Treatment B: Single dose of 6 g FT218 MP4 Batch B Powder for oral suspension, Oral	Dosed in Period 1: 20 Completed: 18	Healthy subjects	Single dose	Completed; Full 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1902	To assess the pharmacokinetics of four 6 g single-doses of once-nightly sodium oxybate (FT218) formulations with varying release rates in healthy volunteers	An open label, randomized, 4-treatment, 4-period, 4-sequence crossover study Control: None	Formulation A: (b) (4) Formulation B: (b) (4) Formulation C: (b) (4) Formulation D: (b) (4) Powder for oral suspension, Oral	Enrolled: 36 Completed: 35	Healthy subjects	Single dose	Completed; Full 5.3.3.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1702	To assess the drug-drug interaction of divalproex sodium extended release (ER) at steady-state on FT218 formulation administered at a single 6 g dose in healthy volunteers	An open-label, sequential study Control: None	Treatment 1: 6 g FT218 Treatment 2: Daily administration of 1250 mg/day divalproex sodium ER to reach steady-state Treatment 3: Co-administration of 1250 mg divalproex sodium ER and 6 g FT218, with divalproex sodium ER administered first Powder for oral suspension, Oral	Enrolled: 24 Completed: 22 Evaluable for PK analysis:21	Healthy subjects	Treatment 1: Day 1 Treatment 2: Days 2-11 Treatment 3: Day 12	Completed; Full 5.3.3.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1901	To assess the drug-drug interaction of divalproex sodium extended release (ER) at steady-state on FT218 formulation administered at a single 6 g evening dose in healthy male volunteers	An open-label, sequential study Control: None	Treatment 1: 6 g FT218 Treatment 2: Daily administration of 1250 mg/day divalproex sodium ER to reach steady-state Treatment 3: Co-administration of 1250 mg divalproex sodium ER and 6 g FT218, with divalproex sodium ER administered first Powder for oral suspension, Oral	Enrolled: 24 Completed: 23	Healthy subjects	Treatment 1: Day 1 Treatment 2: Days 2-11 Treatment 3: Day 12	Completed; Full 5.3.3.1
BA	PKFT218-1601	To assess the pharmacokinetics and safety for sodium oxybate for extended release oral suspension (FT218) formulation after single dose administrations at doses of 4.5, 7.5, and 9 g in healthy volunteers.	An open-label, 3-period study Control: None	Three different doses of FT218 in a sequential order: Treatment A: Single dose 4.5 g FT218 Treatment B: Single dose 6 g FT218 Treatment C: Single dose 9 g FT218 Powder for oral suspension, Oral	Enrolled: 20 Completed: 12	Healthy subjects	Single dose	Completed; Full 5.3.3.4

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy	CLFT218-1501	To assess the efficacy and safety of a once nightly formulation of sodium oxybate for extended-release oral suspension (FT218) for the treatment of excessive daytime sleepiness and cataplexy in subjects with narcolepsy	A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study Control: Placebo	FT218 or placebo, 4 period up-titration: Period 1: FT218 4.5 g or placebo daily for 1 week Period 2: FT218 6.0 g or placebo daily for 2 weeks Period 3: FT218 7.5 g or placebo daily for 5 weeks Period 4: and FT218 9.0 g or placebo daily for 5 weeks. Powder for oral suspension, Oral	As of January 7, 2020, 222 patients have been randomized and 212 dosed. 132 patients have completed the study	Population 1: Subjects with narcolepsy with both EDS and cataplexy (NT1) Population 2: Subjects with narcolepsy with EDS without cataplexy (NT2)	Single dose 13 weeks	Completed; Full 5.3.5.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Efficacy	CLFT218-1901	To Evaluate Long-Term Safety and Tolerability of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) and the ability to switch from twice-nightly immediate release sodium oxybate to once-nightly FT218 for the treatment of excessive daytime sleepiness and cataplexy in subjects with narcolepsy	Open-label Control: None	Subjects Who Completed the REST-ON Study (Group A): Initiate FT218 at 4.5 g Increase by 1.5 g weekly up to 9 g or the dose deemed effective by the Investigator Subjects Currently Receiving Twice-Nightly Sodium Oxybate IR (Group B): Initiate a dose of FT218 equivalent or closest to the total gram dose of twice-nightly sodium oxybate IR dose Titrate up or down, in accord with safety and effectiveness as determined by the Investigator Powder for oral suspension, Oral	Group A: Up to 100 REST-ON participants Group B: Up to 150 subjects currently receiving twice-nightly sodium oxybate	Subjects with narcolepsy, either NT1 or NT2 who completed the Phase 3 RESTON study as well as eligible subjects with narcolepsy currently receiving a stable dose of twice nightly sodium oxybate IR	NA	Ongoing 5.3.5.2

BA = Bioavailability
BE = Bioequivalence
CR = Controlled-release
CSR = Clinical Study Report
IR = Immediate Release
NA = Not applicable
PK = Pharmacokinetic

7.2 Exposure To Sodium Oxybate Extended-Release for Oral Suspension (FT218)

7.2.1 Exposures In Single-Dose Clinical Pharmacology Studies

258 unique subjects were exposed to single doses of FT218 455 times in single-dose clinical pharmacology studies. Their distribution by dose is summarized in the following table.

Daily Dose (g)	Number of Exposures
4.5	63
6	360
7.5	20
9	12

7.2.2 Exposures In Phase 3 Trial CLFT218-1501

212 unique subjects received at least one dose of FT218 in that study. The distribution of those subjects by exposure to individual doses of FT218 in that study is summarized in the following table, which I have copied from the submission.

Daily Dose (g)	Number of Subjects
4.5	97
6	88
7.5	77
9	69

8. Description Of Main Clinical Efficacy Study CLFT218-1501 (REST-ON)

As already noted, this study was conducted under a Special Protocol Agreement, dated October 5, 2016.

The final protocol for that study and the main results of that study (as provided in this submission are summarized below).

8.1 Outline Of Study Protocol

Version 6.0 of Protocol CLFT218-1501, dated July 31, 2019, is summarized below. As already noted, this was the final version of the study protocol.

8.1.1 Title

A Double-Blind, Randomized, Placebo-Controlled, Two-Arm Multicenter Clinical Trial To Assess The Efficacy And Safety Of A Once Nightly Formulation Of Sodium Oxybate for Extended-Release Oral Suspension (FT218) For The Treatment Of Excessive Daytime Sleepiness And Cataplexy In Patients With Narcolepsy.

8.1.2 Objectives

8.1.2.1 Primary Objectives

- To compare the efficacy of FT218 in doses of 6.0 g, 7.5 g, and 9.0 g nightly to placebo in treating excessive daytime sleepiness in patients with Narcolepsy Type 1 (narcolepsy with cataplexy, NT1) and Narcolepsy Type 2 (narcolepsy without cataplexy, NT2), as measured by the Maintenance of Wakefulness Test and Clinical Global Impression ratings.

- To compare the efficacy of FT218 in doses of 6.0 g, 7.5 g, and 9.0 g nightly with placebo in treating cataplexy in patients with Narcolepsy Type 1, as measured by the number of cataplexy attacks, in turn determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary.

8.1.2.2 Secondary/Exploratory Objectives

To compare the efficacy of FT218 in doses of 6.0 g, 7.5 g, and 9.0 g nightly, compared with placebo, on the following:

- Disturbed nocturnal sleep as determined by polysomnographic measurements of sleep fragmentation in patients with Narcolepsy Type 1 and Narcolepsy Type 2.
- Excessive daytime sleepiness in both Type 1 and Type 2 narcolepsy as measured by patient report using the Epworth Sleepiness Scale.
- Number of arousals in both Type 1 and Type 2 narcolepsy as measured by polysomnography.
- Hypnagogic hallucinations and sleep paralysis in Type 1 narcolepsy as recorded in the Sleep and Symptom Diary.

8.1.2.3 Safety Objective

To evaluate the relative safety of FT218 compared with placebo.

8.1.3 Design, Dose, Sample Size, And Duration

This was to be a randomized, double-blind, placebo-controlled, parallel- and two-arm study.

Two populations of patients with narcolepsy were to be studied:

- Patients with excessive daytime sleepiness and cataplexy (Type 1 narcolepsy).
- Patients with excessive daytime sleepiness and no cataplexy (Type 2 narcolepsy).

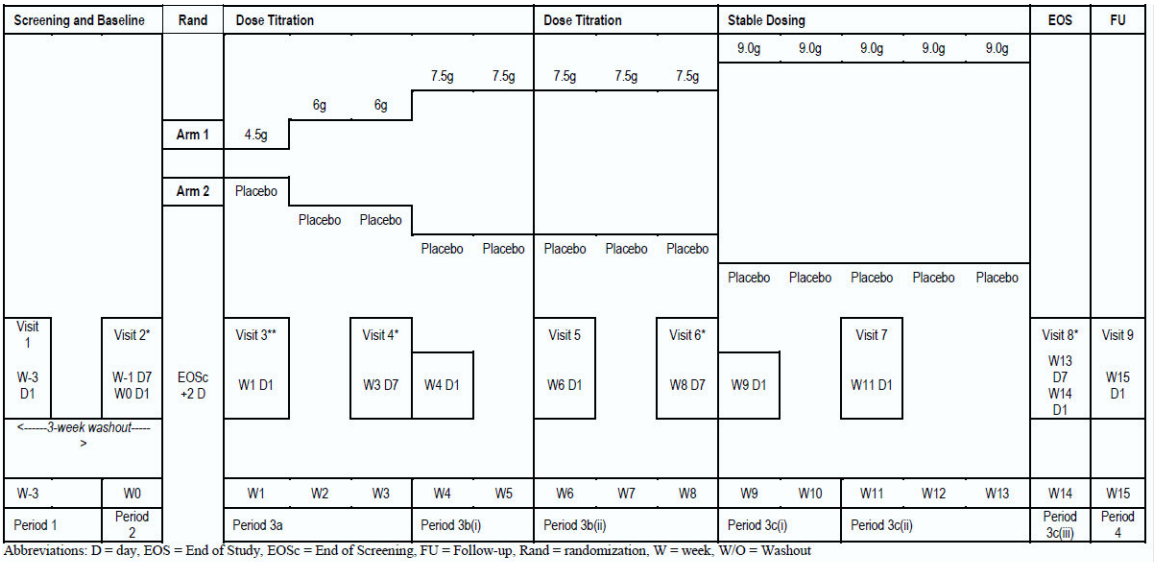
Patients enrolled in the study were to be randomized 1:1 to 2 treatment arms in equal proportions.

- Arm 1: FT218 in a single dose of 9.0 g nightly (final dose, reached after titration).
- Arm 2: Single dose of placebo nightly.

Randomization was to be stratified according to narcolepsy type (i.e., Type 1 or Type 2).

264 patients were to be enrolled in the study and randomized to 2 treatment arms in equal proportions (i.e., 132 patients per treatment arm). A minimum of 107 patients per treatment arm were to have Type 1 narcolepsy.

The study was to have 9 consecutive periods, as outlined in the following table which I have copied from the submission; these 9 consecutive periods were together to be subsumed under the following in succession: a 3-week screening period, a 13-week treatment period, and a 1-week follow-up period. The dose titration schedule for the study is also displayed in the table below.



Abbreviations: D = day, EOS = End of Study, EOSc = End of Screening, FU = Follow-up, Rand = randomization, W = week, W/O = Washout

*Study visits where baseline assessment or full efficacy assessment are done extend into the following day and are thus indicated
**Up to 6 days is allowed between randomization (which occurs 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 is no more than 7 days.)

Forced up-titration was to be used for FT218 and placebo using the schedule depicted above.

Sachets of FT218 powder and placebo powder were to be dissolved in tap water prior to administration at least two hours after the evening meal (instructions were to be provided to each patient as to how each dose of study drug was to be taken).

8.1.4 Key Inclusion Criteria

8.1.4.1 At Screening Visit

- Men and women. Age ≥ 16 years.

- Diagnosis of Type 1 or Type 2 narcolepsy (“NT1” or “NT2,” respectively) based on the following.

    - Results of on overnight polysomnogram and next-day Multiple Sleep Latency test with two or more sleep-onset rapid eye

movement periods and with mean sleep latency in the pathological range of < 8 minutes.

- Excessive daytime sleepiness for at least 3 months and currently presenting with an Epworth Sleepiness Scale score > 10.

The International Classification of Sleep Disorders-3 criteria for NT1 or NT2 must be met.

- Diagnosis of Type 1 narcolepsy, based on presence of cataplexy for at least 3 months (per subject report).

- Evidence of adequate support for the duration of the trial, including transportation to and from the clinical trial site.

- Willingness to adhere to the following restrictions:

  - To remain in bed for a minimum of 6 hours after taking study drug.

  - To adhere to washout requirements for concomitant medication.

  - To refrain from operating a car or heavy machinery if considered necessary by the investigator for at least 6 hours after taking nightly dose of FT218.

  - To abstain from alcohol for the duration of the clinical study.

  - To abstain from smoking at night (from 9 PM to 7 AM) for the duration of the study.

- If a woman of childbearing potential, must be using an appropriate means of contraception: must either agree to use an effective double-barrier method of contraception from the time of signing of the informed consent form through the last dose of study drug, or to completely abstain from heterosexual intercourse. Otherwise, must be post-menopausal for at least one year or surgically sterile.

- Stimulant use permitted, but not required, if dose has been stable for at least 3 weeks before screening and is continued during the trial.

- Written informed consent. Those aged 16 years and 17 years must be capable of assenting to study participation and must have written informed consent provided by a legally authorized representative.

8.1.4.2 At Visit 3 (Randomization)

- Written informed consent, as obtained during the screening visit.
- Continued eligibility as per inclusion criteria at screening visit.
- Compliance with drug washout requirements.
- Compliance in completing study screening and baseline Sleep and Symptom Daily Diary.
- Confirmation of excessive daytime sleepiness as defined by the following:
    - A baseline Epworth Sleepiness Scale score > 10 points.
    - Baseline Maintenance of Wakefulness Test sleep latency score < 11 minutes following baseline polysomnogram and confirmed by central scoring laboratory.
- For those with Type 1 narcolepsy, current continuing presence of cataplexy as defined by an average of 8 reported cataplexy attacks per week in the screening and baseline Sleep and Symptom Daily Diary.
- Negative serum pregnancy test at screening and negative urine pregnancy test within 7 days prior to treatment.

8.1.5 Key Exclusion Criteria

- Prior use of sodium oxybate permitted, but with the following stipulations: previous dosing must have been limited to ≤ 4.5 g/night; previous dosing must not have exceeded 2 weeks; and all previous dosing must not have occurred within the last year prior to study entry.
- Current use of sodium valproate.
- Any use of the following medications: anticonvulsants, clonidine, selective serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, hypnotics, anxiolytics, sedating antihistamines, antipsychotics, or other experimental drugs used to treat narcolepsy or any other condition.
- Treatment with any investigational product within 3 months before enrollment.
- Any drug known to affect sleep-wake function. Stimulant use permitted.
- Diagnosis of sleep apnea or any sleep disorder known to cause excessive daytime sleepiness, as determined by polysomnography and sleep history, including any results indicating an apnea-hypopnea index ≥ 15.
- Presence of any unstable or clinically significant medical and psychiatric disorders (as determined by history, physical examination, and/or

laboratory tests) which in the opinion of the investigator may either put the subject at risk or may influence the results of the study.

- Previous history of, or current, suicidal ideation or a suicide attempt
- History of drug or alcohol use that in the opinion of the investigator would interfere with subject safety and adherence to study requirements.
- Required commercial or other driving during study period.
- Any occupation requiring variable shift work or routine night shifts.
- Any travel across more than 3 time zones during the course of the study.
- Consuming more than 14 standard alcoholic drinks per week, on average, before participating in the clinical research study.
- Smoking at night (between 9 PM and 7 AM) during the course of the study.

And the following:

- Female subjects currently lactating or with a positive pregnancy test. Females of reproductive potential not willing or able to employ effective methods of birth control/contraception to prevent pregnancy for the duration of the study and for up to 1 week after completing study treatment.
- Any current malignancy and/or any history of malignancy within last 3 years.
- A history of seizure disorder, head trauma, or past invasive intracranial surgery.
- Subjects with severe chronic obstructive pulmonary disease. Subjects with mild to moderate chronic obstructive pulmonary disease and assessed as stable by the Principal Investigator were to be eligible. Principal Investigator judgement was to be used regarding other underlying respiratory and/or other underlying condition or disorder that would potentiate the risk of respiratory or central nervous system depression with concomitant use of sodium oxybate.
- Known hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection.
- Known human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness.
- Scheduled for procedures requiring general anesthesia during the study.
- Known contraindication/allergy/sensitivity/intolerance to the study drug, sodium oxybate, or the inactive ingredients of FT218 or placebo.
- Atrial fibrillation or an abnormal electrocardiogram demonstrating clinically significant dysrhythmia(s).
- Recent myocardial infarction or coronary revascularization procedure (less than 3 months before entry).
- Uncontrolled hypertension.
- Known succinic semi-aldehyde dehydrogenase deficiency.

- Moderately or severely altered blood chemistry as defined by any one of the following:
  - A Cockcroft-Gault calculated creatinine clearance < 60 mL/min; OR
  - Liver function tests more than twice the upper limit of normal; OR
  - Serum bilirubin more than 1.5 times the upper limit of normal.

8.1.6 Concomitant Medications

See Exclusion Criteria above.

8.1.7 Schedule

A detailed schedule for the study is in the table below, which I have copied from the study protocol.

	Period 1	Period 2	Randomization*	Period 3a	Period 3b(i)	Period 3b(ii)	Period 3c(i)	Period 3c(ii)	Period 3c(iii)	Period 4
Overarching Weeks	Weeks -3 to 0	Week 0		Weeks 1 to 3	Weeks 4 to 5	Weeks 6 to 8	Weeks 9 to 10	Weeks 11 to 13	Week 14	Week 15
Visit	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EOS)	Visit 9
Day of Visit	W-3 D1	W-1 D7 W0 D1		W1 D1	W3 D7 W4 D1	W6 D1	W8 D7 W9 D1	W11 D1	W13 D7 W14 D1	W15 D1 (+4/-0)
Informed consent	X									
Inclusion and exclusion criteria	X	X		X						
Demographics	X									
Study restriction questions[1]	X§	X§		X	X	X	X	X	X	
Medical, surgical & psychiatric history	X									
Physical examination	X	X‡		X‡	X‡	X‡	X‡	X‡	X	X‡
Vital signs[2]	X	X		X	X	X	X	X	X	X‡
Weight, height & BMI[3]	X			X					X	X
**Clinical laboratory (biochemistry & hematology)	X	X							X	X‡
Serology (HBsAg, anti-HCVAb)	X									
Pregnancy test[4]	X	X		X	X	X	X	X	X	X
**Urinalysis	X	X							X	
Urine drug screen[5]	X	X‡		X‡	X‡	X‡	X‡	X‡	X‡	
**12-lead ECG	X								X	
Assessment of prior or current drug abuse & dependence	X§	X§		X	X	X	X	X	X	
Narcolepsy diagnosis by type (NT1/NT2)[6]	X									
ESS	X[7]	X			X	X	X	X	X	
C-SSRS	X	X		X	X	X	X	X	X	

	Period 1	Period 2	Randomization*	Period 3a	Period 3b(i)	Period 3b(ii)	Period 3c(i)	Period 3c(ii)	Period 3c(iii)	Period 4
Overarching Weeks	Weeks -3 to 0	Week 0		Weeks 1 to 3	Weeks 4 to 5	Weeks 6 to 8	Weeks 9 to 10	Weeks 11 to 13	Week 14	Week 15
Visit	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EOS)	Visit 9
Day of Visit	W-3 D1	W-1 D7 W0 D1		W1 D1	W3 D7 W4 D1	W6 D1	W8 D7 W9 D1	W11 D1	W13 D7 W14 D1	W15 D1 (+4/-0)
Obstructive sleep apnea (OSA)[8]	X									
§Confirmation subject is educated on and understands washout requirements	X									
Confirmation of washout compliance[9]		X§		X	X	X	X	X	X	
PSG[10]		X†			X		X		X	
MWT[11]		X†			X		X		X	
Central scoring laboratory: PSG & MWT eligibility assessment[12]		X								
CGI[13]		X			X	X	X	X	X	
Provision of ePRO device	X									
Education & training on ePRO device[14]	X			X	X	X	X	X		
Review of Baseline ePRO: • Narcolepsy and Sleep and Symptom Daily Diary • Confirmation of continued cataplexy for NT1 subjects • ESS questionnaire		X§								
Return & storage of ePRO device at site									X	
Review and confirmation of ePRO diary: • Self-recorded study drug compliance record (with returns check) • ESS questionnaire • Completed Sleep and Symptom Daily Diary from previous period					X	X	X	X	X	
Update IRT system[15]	X	X		X	X	X	X	X	X	
Drug dispensing[16]				X	X	X	X	X		

	Period 1	Period 2	Randomization*	Period 3a	Period 3b(i)	Period 3b(ii)	Period 3c(i)	Period 3c(ii)	Period 3c(iii)	Period 4
Overarching Weeks	Weeks -3 to 0	Week 0		Weeks 1 to 3	Weeks 4 to 5	Weeks 6 to 8	Weeks 9 to 10	Weeks 11 to 13	Week 14	Week 15
Visit	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (EOS)	Visit 9
Day of Visit	W-3 D1	W-1 D7 W0 D1		W1 D1	W3 D7 W4 D1	W6 D1	W8 D7 W9 D1	W11 D1	W13 D7 W14 D1	W15 D1 (+4/-0)
Drug accountability[17]					X	X	X	X	X	
Schedule next visit	X	X		X	X	X	X	X	X	
Adverse events		X		X	X	X	X	X	X	X[18]
Concomitant medications[19]	X	X		X	X	X	X	X	X	X[18]
Off-study treatment discussion[20]										X

Abbreviations: BMI = body mass index, CGI = clinical global impression, C-SSRS = Columbia-Suicide Severity Rating Scale, D = day, ECG = electrocardiogram, EOS = end of study, ePRO = electronic patient reported outcome, ESS = Epworth Sleepiness Scale, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, IRT = interactive response technology, MWT = Maintenance of Wakefulness Test, NT1 = type 1 narcolepsy, NT2 = type 2 narcolepsy, PI = principal investigator, PSG = polysomnography, W = week

* Randomization is not a subject visit. Randomization is performed by the PI immediately after receipt of the central scoring assessment of PSG and MWT (≤ 2 days), and determination that the subject is eligible based on the central scoring result. Subjects will be stratified according to narcolepsy type NT1/NT2 in a 1:1 fashion to 1 of the 2 treatment arms. The PI/designee enters the information into the IRT system, and the appropriate study drug is sent to the site. Study treatment must begin within 6 days of randomization, depending on the time taken for receipt of the central scoring assessment. Total time between PSG and MWT and dosing should not exceed 7 days.

** Repeat of these procedures are applicable only if clinically indicated by the PI

§ These assessments must be performed first to ensure criteria are fulfilled before the rest of visit procedures are performed

† Perform if all other assessments at this visit are satisfactory

‡ Perform if clinically indicated by the PI

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following training and education session the subject will be informed and withdrawn from study and an unscheduled visit will be performed.

1 Assess alcohol, caffeine, and nicotine consumption and subject agreement to adhere to study mandated restrictions during the study at Visit 1. At all other indicated visits, assess compliance with smoking restrictions (as applicable), abstinence from alcohol, and all other study restrictions

2 Systolic and diastolic BP and heart rate are recorded

3 Weight (kg), height (cm), BMI (kg/m²). Height and BMI will be measured at screening only

4 Serum pregnancy test to be performed at Visit 1, urine pregnancy test to be performed at all other visits

5	Drug screen includes benzodiazepines, cannabis, cocaine, opiates, and barbiturates
6	Confirmation of NT1 or NT2. A copy of all diagnostic records for narcolepsy, including overnight PSG and next-day MSLT must be filed. Confirmation from historical PSG that subject did not have AHI ≥ 15
7	Epworth Sleepiness Scale is completed on a printed version at screening (Visit 1). At all other visits it is performed with the ePRO device
8	Conduct measurement of subject's neck circumference and document snoring patterns. Criteria will be assessed relative to ESS score, BMI, BP, age, and gender. A determination on eligibility to proceed through the screening period will be made relative to OSA risk. PIs will be trained on this at Site Initiation. In the event that following completion of the assessment the risk for OSA goes undetected, confirmation of the presence of OSA will be detected on overnight PSG (AHI ≥ 15) at Week 3 in the screening and baseline period of the study. Where OSA is detected, the subject will be withdrawn from study.
9	Total washout period: 3-week washout (from screening visit, Week -3, Day 1 to Visit 2, Week 0); subjects to remain off prohibited concomitant medication for 3 weeks before final aggregated subject assessment for eligibility to the double-blind period. Subjects will remain off these medications for the duration of the clinical study. Subjects are educated on compliance requirements and symptom management during this period and for the duration of the study and will be given all necessary emergency contact numbers at site. Subjects are advised they can contact the site at any time should they have any questions or concerns
10	Overnight 8 hour PSG
11	Next-day MWT (5 hour nap)
12	Overnight PSG and next-day MWT for eligibility will be performed at the end of the 3-week screening period(Week -1, Day 7 overnight to Week 0 Day 1) after all other assessments have been performed at Visit 2 and the results are satisfactory. The results from the PSG and MWT assessments will be analyzed by the central scoring laboratory. It will take a maximum of 2 days for results to be returned to the PI
13	CGI assessment of severity of sleepiness at Visit 2, and subsequently assessment of improvement in sleepiness (investigator blinded to MWT results)
14	Training instructions given on ePRO Sleep and Symptom Daily Diary completion requirements and on its use as it relates to study protocol diary records, drug adherence records and notifications on all other subject facing applications. Consequences of poor compliance will be discussed
15	At Visit 1, the IRT system is updated with subject details, planned Visit 2 date, and planned dates for PSG and MWT. At all other indicated visits, the IRT system is updated with subject details for next visit and study drug returns. At Visit 8, the IRT is updated with EOS details and subject drug accountability
16	Prior to dispensing, subject must be assessed for compliance with drug handling, management, and safety requirements including a check that subject is eating at least 2 hours before taking study drug. Education & training on study drug reconstitution, management, self-care and safety occurs at Visit 3 and re-education on study drug safety and handling at all other dispensing visits, if deemed necessary by the PI
17	At Visit 8, reconciliation is also performed with drug accountability as well as subject compliance with drug handling, management, and safety requirements
18	All AEs and concomitant medications reviewed and assessment for residual effects of study drug. If the subject is unable to return to the clinic, a phone call must occur to assess AEs or residual effects of study drug and concomitant medication
19	Document medication taken 30 days prior to Visit 1. At all other visits, document concomitant medication taken since last visit. Adherence to prohibited medication requirements must be assessed & documented
20	Discuss off-study narcolepsy therapeutic pathway with subject

8.1.8 Outcome Measures

8.1.8.1 Primary Efficacy Measures

8.1.8.1.1 For Evaluating Excessive Daytime Sleepiness (NT1 And NT2)

Maintenance of Wakefulness Test score (mean latency averaged across 5 naps on the day of testing).

Clinician Global Impression of Improvement (clinician's impression of change in excessive daytime sleepiness from baseline).

8.1.8.1.2 For Evaluating Cataplexy (NT1 Only)

Mean number of weekly cataplexy attacks from Sleep and Symptom Daily Diary.

(A minimum number of diary entries of 3 per week were to be required for the average to be considered an observation. If the number of entries for that week was less than three, the mean daily cataplexy frequency for that week was to be considered missing).

8.1.8.2 Secondary Efficacy Measures

- Disturbed nocturnal sleep based on polysomnography: number of shifts from Stage 1 (N1), Stage 2 (N2), Stage 3 (N3), and the rapid eye movement (REM) stage, to wake; and number of shifts from the N2, N3, and REM stages to the N1 stage.

- Epworth Sleepiness Scale score.

- Number of transient arousals on nocturnal polysomnogram as defined by the American Academy of Sleep Medicine scoring guidelines for nocturnal polysomnography.

- Quality of sleep as measured by visual analog scale (mean of responses to refreshing nature of sleep in the Sleep and Symptom Daily Diary) averaged over the 14 days preceding the test day.

- Number of hypnagogic hallucination events recorded in the Sleep and Symptom Daily Diary averaged over the 14 days preceding the test day.

- Number of sleep paralysis events recorded in the Sleep and Symptom Daily Diary averaged over the 14 days preceding the test day.

8.1.8.3 Safety Measures

Adverse events, vital signs, safety laboratory tests, electrocardiogram, physical examinations, and Columbia-Suicide Severity Rating Scale.

8.1.9 Further Description Of Primary Efficacy Measures

The primary efficacy measures that were to be used in this study are summarized below.

For details of the secondary efficacy measures used, please refer to the study protocol itself. As would be expected, these were to be derived from polysomnography, the daily Sleep and Symptom Diary, and patient-rated assessments such as the Epworth Sleepiness Scale and the visual analog scale assessing quality of sleep.

8.1.9.1 Maintenance Of Wakefulness Test

The Maintenance of Wakefulness Test measures latency (in minutes) to sleep onset, averaged over 5 sessions (naps) at 2-hour intervals, using polysomnography. The test is conducted during a period of inactivity. For each test session, the subject is asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 5 sessions.

8.1.9.2 Clinical Global Impression Of Improvement

This ordinal instrument was intended to assess the severity of sleepiness at post-baseline visits as compared with baseline. This instrument was evaluated on a 7-point scale that extended from a score of 7 (“Very Much Worse”) to 1 (“Very Much Improved,”) but was centered at 0 (“No Change”).

8.1.9.3 Weekly Frequency Of Cataplexy Attacks

The weekly frequency of cataplexy attacks was to be based on the patient-recorded electronic Sleep and Symptom Daily Diary.

8.1.10 Analysis Plan For Primary Efficacy Analysis

A mixed model for repeated measures was to be used to analyze the change from baseline for the Maintenance of Wakefulness Test mean sleep latency score and the weekly frequency of cataplexy attacks.

For the Clinician Global Impression of sleepiness (clinician's impression of change in excessive daytime sleepiness from baseline), the difference in the proportion of patients who were either much improved or improved on that 7-point scale was to be compared (as the primary analysis) using a GLIMMIX model for binomial data with logit link.

These analyses were to compare the 9.0 g/night, 7.5 g/night, and 6.0 g/night doses with placebo. Each model was to include treatment, time, treatment-by-time interaction, site and baseline score as fixed effects, and subjects as random effects.

The modified intent-to-treat population to be used for the primary efficacy analysis directed at excessive daytime sleepiness was to consist of all randomized subjects with both NT1 and NT2 with at least one efficacy assessment after receiving the 6.0 g/night dose. The modified intent-to-treat population to be used for the primary efficacy analysis directed at cataplexy frequency was to consist of all randomized subjects with NT1 only with at least one efficacy assessment after receiving the 6.0 g/night dose.

The per protocol population, which was to be used for additional (supportive) efficacy analyses, was to consist of all randomized patients minus those with protocol deviations.

Sensitivity analyses were to be performed on the primary mixed-effects repeated measures model.

The sequence of hypothesis testing to be used is summarized below.

8.1.10.1 Sequence Of Hypothesis Testing For Primary Efficacy Endpoints

The primary hypothesis tests for the individual doses was to be performed as contrasts within the mixed models to be used. The hypothesis tests were be performed in the following numerical order, each at a significance level of 0.05 (two-sided).

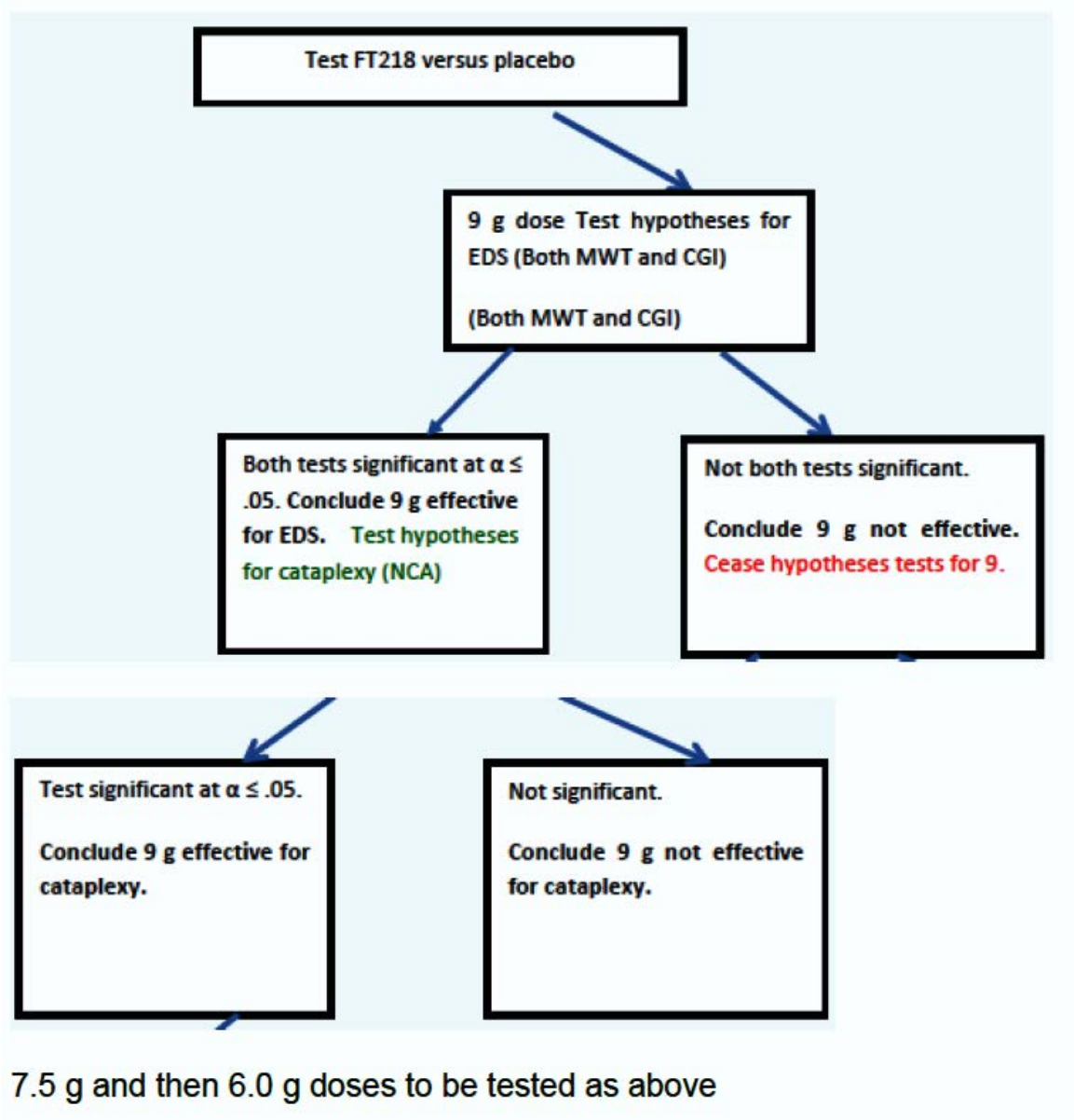
The 9 g/day dose of FT218 was first to be compared with placebo on the change from baseline in Maintenance of Wakefulness Test mean sleep latency score and Clinical Global Impression of Change using data collected in Periods 3c(i) and 3c(ii). If only one or neither of those comparisons was statistically significant, the 9.0 g/day dose was to be considered not to be superior to placebo for either of those measures, and further hypothesis testing was not to be performed. If both the above comparisons were statistically significant and in favor of FT218, the 9.0 g/day dose of FT218 was to be considered effective in the treatment of excessive daytime sleepiness in narcolepsy, and the 9.0 g/day dose of FT218 was then to be compared with placebo on the change from baseline in daily cataplexy score; if the latter comparison was statistically significant and in favor of FT218, the 9.0 g/day dose of FT218 will also be considered effective for treating cataplexy.

The same sequence of tests was then to be performed for the 7.5 g/day and then the 6.0 g/day doses of FT218.

(Per the already-described forced titration schedule for this study, the 6.0 g/day dose was to be administered during Weeks 2 and 3, the 7.5 g/day dose from Week 4 through Week 8, and the 9.0 g/day dose from Week 9 through Week 13).

Rejection at any step was to terminate all further steps of the testing sequence.

The planned sequence of hypothesis testing is in the applicant-provided graphic (amended slightly by this reviewer) below.



8.1.11 Analyses Of Secondary And Exploratory Endpoints

These were to be analyzed using measures similar to those used for the primary efficacy analysis.

8.1.12 Analyses Of Safety Endpoints

The safety population was to consist of all subjects who received at least one dose of study medication.

Adverse events and laboratory data were to be summarized using standard methods. For a description of other aspects of the planned safety analysis, please see the study protocol.

8.1.13 Sample Size Estimate For Study

The sample size estimate for this study was based on assumptions for treatment differences on the three primary efficacy variables following a review of the medical literature for Xyrem.

- A difference between the FT218 and placebo groups in the mean change from baseline to endpoint in the Maintenance of Wakefulness Test score of 3.3 with a standard deviation of 5.1.

- 60% of patients receiving FT218 being much improved or very much improved on the Clinical Global Impression of sleepiness versus 25% of patients who received placebo.

- A difference of 16 between the FT218 and placebo groups in the mean number of cataplexy episodes per week with a standard deviation of 16.5.

Based on the above assumptions and a two-sided alpha of 0.05, 70 patients per treatment group evaluated for the Maintenance of Wakefulness Test and Clinical Global Impression of Change in sleepiness and 50 patients per group evaluated for the frequency of cataplexy attacks would provide:

- 96% power for the Maintenance of Wakefulness Test.

- 99% power for Clinical Global Impression of sleepiness.

- 85% power for the weekly frequency of cataplexy attacks.

- Overall, 81% power for all 3 endpoints, assuming that the endpoints are independent of each other.

Based on the above sample size estimate, enrollment was to continue until a completer projection estimated that that there would be 70 patients for evaluation on the Maintenance of Wakefulness Test and Clinical Global Impression of Change in sleepiness, and 50 patients evaluable for the frequency of cataplexy attacks.

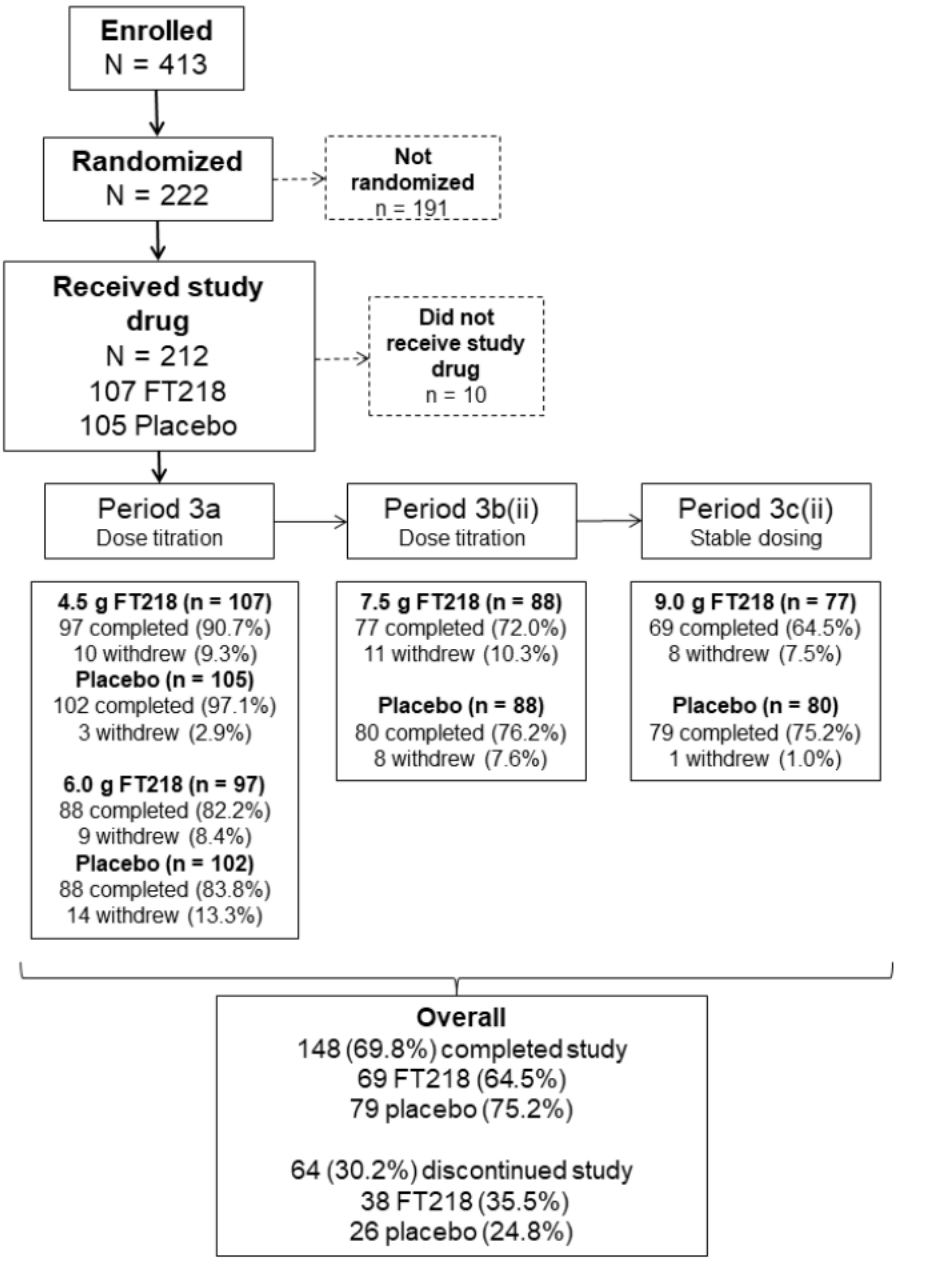
8.2 Study Results

The study, which was conducted in the United States, United Kingdom, Australia, and Canada, appears to have been conducted in a manner consistent with the final version of the clinical protocol.

8.2.1 Patient Disposition

413 patients were enrolled in the study, of whom 222 patients were randomized; of the patients randomized, 212 received at least one dose of study medication. 148 subjects (69.8% of those randomized) completed the study.

The following flowchart, copied from the submission, summarizes patient disposition across the study.



Further details about patient disposition are provided in the following table, which I have copied from the submission. As the table indicates, the majority of those in

the modified intent-to-treat population had narcolepsy Type 1. The table also provides reasons for subject discontinuation, and is self-explanatory in that regard.

Category	FT218 N = 111	Placebo N = 111	Overall N = 222
Enrolled by signing informed consent	–	–	413
Randomized	111	111	222
Safety population, n (%)	107 (96.4)	105 (94.6)	212 (95.5)
mITT population, n (%)	97 (87.4)	93 (83.8)	190 (85.6)
mITT (NT1) population, n (%)	73 (65.8)	72 (64.9)	145 (65.3)
Per protocol population, n (%)	76 (68.5)	81 (73.0)	157 (70.7)
Per protocol (NT1) population, n (%)	55 (49.5)	61 (55.0)	116 (52.3)
Overall (safety population)	FT218 N = 107	Placebo N = 105	Overall N = 212
Completed study, n (%)	69 (64.5)	79 (75.2)	148 (69.8)
Discontinued study, n (%)	38 (35.5)	26 (24.8)	64 (30.2)
Adverse event	21 (19.6)[1]	3 (2.9)	24 (11.3)
Withdrawal by subject	11 (10.3)	11 (10.5)	22 (10.4)
Lack of efficacy	2 (1.9)	8 (7.6)	10 (4.7)
Other	2 (1.9)[2]	1 (1.0)[3]	3 (1.4)
Pregnancy	2 (1.9)	0	2 (0.9)
Protocol deviation	0	2 (1.9)	2 (0.9)
Noncompliance with study drug	0	1 (1.0)	1 (0.5)

Source: Table 14.1.1 and Listing 16.2.1.1
Abbreviations: mITT = modified intent-to treat; NT1 = type 1 narcolepsy
[1] Does not include the two FT218-treated subjects who discontinued due to pregnancy (Section 12.5.3.3).
[2] Subject lost to follow-up.
3 Subject took an excluded concomitant medication (Wakix®).
Note: Subjects who completed all treatments and the last scheduled visit were considered as completing the study.

8.2.2 Protocol Deviations

The numbers and proportions of those patients in the safety population who had major protocol deviations are summarized in the next applicant table.

Category	FT218 N = 107 n (%)	Placebo N = 105 n (%)	Overall N = 212 n (%)
Subjects with at least one type of significant protocol deviation, n (%)	22 (20.6)	13 (12.4)	35 (16.5)
Subjects' procedures not per protocol and affected interpretation of primary objectives and/or affected patient safety	9 (8.4)	8 (7.6)	17 (8.0)
Received excluded concomitant medication/treatment	4 (3.7)	5 (4.8)	9 (4.2)
Study entry without meeting entry criteria	6 (5.6)	3 (2.9)	9 (4.2)
Wrong treatment or incorrect dose[1]	6 (5.6)	2 (1.9)	8 (3.8)
Procedures and tests, not affecting interpretation of primary study objectives and/or affect patient safety[2]	1 (0.9)	0	1 (0.5)

Source: Table 14.1.2
[1] No subjects received the wrong treatment.
[2] The deviation for Subject (b) (6) was reported in the incorrect category. The subject took the selective serotonin reuptake inhibitor vortioxetine, a prohibited medication, for the duration of their participation in the study. The category associated with this deviation was mistakenly reported as "Procedures and tests, not affecting interpretation of primary study objectives and/or affect patient safety" but the correct deviation category is "Received excluded concomitant medication/treatment."

8.2.3 Demographic And Other Baseline Characteristics

The demographic and baseline characteristics of the safety population are summarized in the following table, which I have copied from the submission.

As the table indicates, most patients enrolled in this study had narcolepsy Type 1; i.e., narcolepsy with cataplexy.

Category	FT218 N = 107	Placebo N = 105	Overall N = 212
Age (years)			
Mean (SD)	30.9 (10.70)	31.6 (11.24)	31.2 (10.95)
Median (range)	29.0 (16-72)	30.0 (16-69)	29.0 (16-72)
Gender, n (%)			
Female	69 (64.5)	75 (71.4)	144 (67.9)
Male	38 (35.5)	30 (28.6)	68 (32.1)
Race, n (%)			
White	80 (74.8)	80 (76.2)	160 (75.5)
Black/African American	21 (19.6)	15 (14.3)	36 (17.0)
Asian	3 (2.8)	8 (7.6)	11 (5.2)
Other[1]	3 (2.8)	2 (1.9)	5 (2.4)
Region, n (%)			
United States	63 (58.9)	53 (50.5)	116 (54.7)
Rest of world	44 (41.1)	52 (49.5)	96 (45.3)
Height (cm)			
Mean (SD)	170.3 (8.7)	170.0 (10.1)	170.1 (9.4)
Median (range)	170.2 (147.3-193.0)	168.0 (148.0-195.0)	169.5 (147.3-195.0)
Weight (kg)			
Mean (SD)	81.2 (20.8)	82.1 (22.5)	81.6 (21.6)
Median (range)	77.6 (47.0-162.0)	79.0 (48.0-156.0)	78.3 (47.0-162.0)
Body mass index (kg/m^2)			
Mean (SD)	28.1 (7.8)	28.2 (6.6)	28.1 (7.2)
Median (range)	26.1 (16.9-71.9)	26.4 (18.1-46.5)	26.4 (16.9-71.9)
Narcolepsy type, n (%)			
NT1	80 (74.8)	82 (78.1)	162 (76.4)
NT2	27 (25.2)	23 (21.9)	50 (23.6)

Source: Table 14.1.3 and Listing 16.2.4.1.1
Abbreviations: NT1 = type 1 narcolepsy; NT2 = type 2 narcolepsy; SD = standard deviation
[1] Egyptian (n = 2), White, American Indian/ Alaska Native (n = 1), half Asian, half White (n = 1), and biracial (White/African-American/Native American, n = 1)

8.2.4 Concomitant Medications

Concomitant medications taken by ≥ 5% of patients overall in the safety population are summarized in the next applicant table, which is self-explanatory.

WHO Drug Dictionary preferred term	FT218 N = 107 n (%)	Placebo N = 105 n (%)	Overall N = 212 n (%)
Modafinil	23 (21.5)	22 (21.0)	45 (21.2)
Ibuprofen	16 (15.0)	16 (15.2)	32 (15.1)
Paracetamol	17 (15.9)	10 (9.5)	27 (12.7)
Armodafinil	13 (12.1)	7 (6.7)	20 (9.4)
Dexamfetamine sulfate	10 (9.3)	8 (7.6)	18 (8.5)
Amfetamine aspartate/amfetamine sulfate/dexamfetamine saccharate/dexamfetamine sulfate	11 (10.3)	6 (5.7)	17 (8.0)
Ascorbic acid/colecalciferol/nicotinamide/pyridoxine hydrochloride/retinol/riboflavin/thiamine hydrochloride (multivitamin)	7 (6.5)	6 (5.7)	13 (6.1)
Ergocalciferol (vitamin D)	7 (6.5)	4 (3.8)	11 (5.2)
Lisdexamfetamine mesilate	5 (4.7)	6 (5.7)	11 (5.2)
Methylphenidate hydrochloride	11 (10.3)	7 (6.7)	18 (8.5)

8.2.5 Treatment Compliance

The extent of treatment compliance is summarized in the next applicant table, which is again self-explanatory.

Period	FT218 N = 107 n (%)	Placebo N = 105 n (%)	Overall N = 212 n (%)
Overall study[1]	n = 106	n = 104	n = 210
Mean (SD)	83.3 (27.64)	90.9 (19.77)	87.1 (24.31)
Period 3a, 4.5 g FT218 or placebo	n = 106	n = 104	n = 210
Mean (SD)	94.2 (16.79)	96.50 (13.58)	95.34 (15.29)
Period 3a, 6.0 g FT218 or placebo	n = 106	n = 104	n = 210
Mean (SD)	84.1 (31.34)	91.1 (22.08)	87.6 (27.31)
Period 3b (i and ii), 7.5 g FT218 or placebo	n = 88	n = 89	n = 177
Mean (SD)	92.0 (21.74)	95.1 (14.05)	93.5 (18.30)
Period 3c (i and ii), 9.0 g FT218 or placebo	n = 77	n = 80	n = 157
Mean (SD)	92.5 (16.37)	96.8 (10.80)	94.7 (13.93)

Source: Table 14.1.5
Abbreviations: SD = standard deviation
[1] Compliance data are not available for two subjects who prematurely discontinued, one from the FT218 group who was lost to follow-up (last visit Day 33) and one placebo-treated subject who withdrew consent on Day 5.
Note: Treatment compliance (%) was calculated as follows: 100 * total number of used sachets/total number of dispensed sachets.

8.2.6 Efficacy Results

8.2.6.1 Primary Efficacy Analysis

(As has already been pointed out, per the forced titration schedule for this study, the 6.0 g/day dose was to be administered during Weeks 2 and 3, the 7.5 g/day dose from Week 4 through Week 8, and the 9.0 g/day dose from Week 9 through Week 13).

As the following tables make clear, FT218 demonstrated a statistically significant superiority over placebo ($p < 0.0001$) on all three primary efficacy parameters, the Maintenance of Wakefulness Test mean sleep latency, the Clinical Global Impression of Sleepiness, and the mean weekly number of cataplexy attacks; this effect was apparent at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day). These results indicate FT218 had efficacy in the treatment of both cataplexy and excessive daytime sleepiness in narcolepsy and that those effects were clinically meaningful.

(As the following tables make clear, the treatment groups were comparable on each of the primary efficacy measures at baseline).

8.2.6.1.1 Maintenance Of Wakefulness Test Mean Sleep Latency

The results of the applicant's analysis of the Maintenance of Wakefulness Test mean sleep latency outcome are displayed in the following applicant table and are self-explanatory. They confirm the statistically significant superiority of FT218 over placebo on this instrument at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day) as has already been stated above.

Table 18 MWT Mean Sleep Latency Change from Baseline (Minutes) to the End of Each Treatment Period (MMRM Analysis, 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)	—	—	—

Source: Tables 14.2.1.1.1, 14.2.1.2.1, 14.2.1.3.1, and 14.2.1.4.1
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; MWT = Maintenance of Wakefulness Test; SD = standard deviation; SE = standard error
[1] P-value estimated using an MMRM with change from baseline as the response variable, fixed effects of treatment, visit, treatment by visit, site (United States or Non-United States), covariate of baseline MWT score, subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were < 0.001.
Note: MWT is the mean latency across 5 naps, averaged over the test day. If the number of naps was < 3, the MWT was considered missing.

8.2.6.1.2 Clinical Global Impression Of Sleepiness

The results of the applicant's analysis of the Clinical Global Impression of Sleepiness (Improvement) are displayed in the following table and are again self-explanatory. They confirm the statistically significant superiority of FT218 over placebo on this instrument at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day) as has already been stated above.

Table 19 Summary of CGI of Sleepiness over Time (GLIMMX Model, 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	—	—	—

Source: Tables 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, and 14.2.2.4.1
Abbreviations: CGI = Clinical Global Impression; CI = confidence interval; mITT = modified intent-to-treat
[1] P-values were estimated by the GLIMMIX model with categorized CGI-Improvement response (very much or much improved versus other category) at the specific visit as the response variable, fixed effects of treatment, visit, treatment by visit, site (United States or Non-United States), and subjects as random effect.
[2] Two subjects (one in each treatment group) did not have a baseline measurement.
Note: CGI-Severity ranged from 1 (normal, not at all sleepy) to 7 (among the most extremely sleepy patients). CGI-Improvement ranged from 1 (very much improved) to 7 (very much worse).

8.2.6.1.3 Number Of Cataplexy Attacks

The results of the applicant's analysis of the weekly frequency of cataplexy attacks are displayed in the following applicant table and are again self-explanatory. They confirm the statistically significant superiority of FT218 over placebo on this instrument at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day) as has already been stated above.

This analysis was conducted, per protocol, only in those subjects who had narcolepsy Type 1.

Table 20 Mean Weekly NCA of Each Dosing Period (MMRM Analysis, NT1 Subjects in the 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: Tables 14.2.3.1.1, 14.2.3.2.1, 14.2.3.3.1, and 14.2.3.4.1
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; NCA = number of cataplexy attacks; NT1 = type 1 narcolepsy; SD = standard deviation; SE = standard error
[1] P-value estimated using an MMRM with change from baseline to the end of the respective treatment period as the response variable, fixed effects of treatment, visit, treatment by visit, site (United States or Non-United States), covariate of baseline weekly NCA score, subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were < 0.001.
Note: The NCA were events recorded on the Sleep and Symptom Daily Diary. NCA reported as "Five or more times" were calculated as five events for the purpose of quantitative summaries. For each period, the mean weekly NCA was calculated as the number of NCA divided by the number of days with available diary data of valid weeks within that period then multiplied by 7. If a week had < 3 Diary records, that week was considered invalid and was not used to calculate the mean weekly NCA. The baseline period was the 3 weeks between Visit 1 and Visit 2. If the screening and baseline periods were > 21 days, baseline was defined as the last 21 days up to Visit 2.

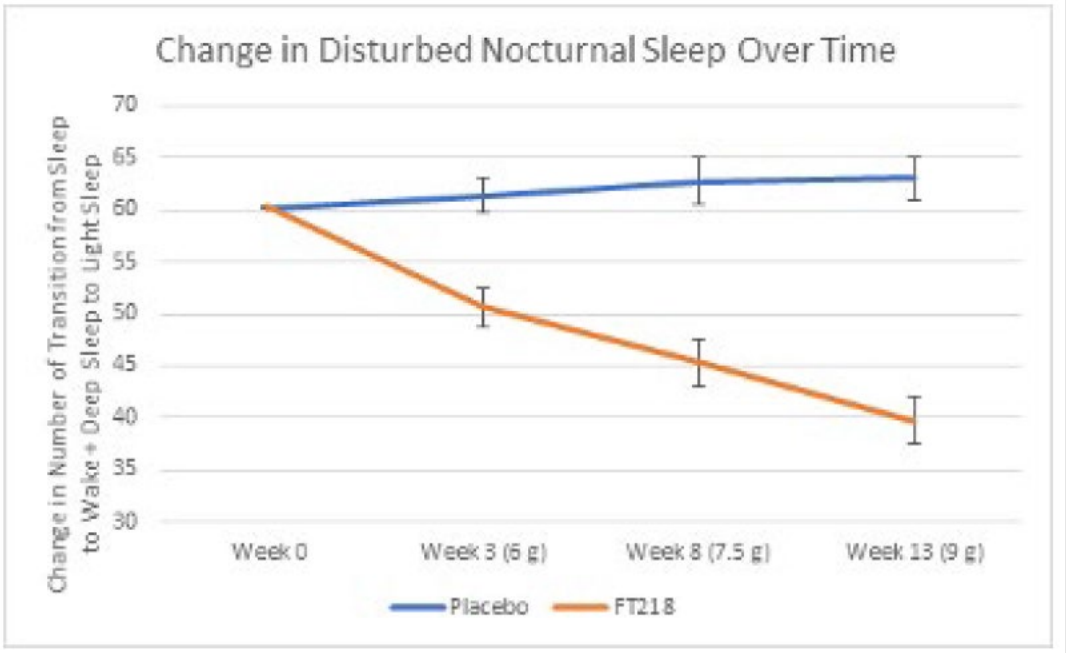
8.2.6.2 Analysis Of Secondary Efficacy Measures

8.2.6.2.1 Disturbed Nocturnal Sleep Score

The results of the applicant's analysis of the disturbed nocturnal sleep score are displayed in the following applicant table and figure, which are self-explanatory. They indicate an effect of FT218 over placebo on this instrument at a nominally statistically significant at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day).

The analysis is based on a mixed model for repeated measures using the modified intent-to-treat population.

Dose	Treatment Group (N)	Baseline Score (SD)	Change from Baseline (SE)	Difference from Placebo [95% CI]	p-value
6 g (Week 3)	FT218 (88)	60.1 (23.37)	-9.69 (1.82)	-11.00 [-16.07;-5.93]	<0.001
	Placebo (88)	60.3 (21.77)	1.31 (1.81)	-	-
7.5 g (Week 8)	FT218 (76)	60.1 (23.37)	-15.00 (2.32)	-17.70 [-24.12;-11.28]	<0.001
	Placebo (79)	60.3 (21.77)	2.70 (2.27)	-	-
9 g (Week 13)	FT218 (69)	60.1 (23.37)	-20.54 (2.19)	-22.63 [-28.60,--16.66]	<0.001
	Placebo (78)	60.3 (21.77)	2.09 (2.09)	-	-



8.2.6.2.2 Epworth Sleepiness Scale Score

The results of the applicant's analysis of the Epworth Sleepiness Scale score are displayed in the following applicant table, which is self-explanatory. They indicate an effect of FT218 over placebo on this instrument at a nominally statistically significant level at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day). The results are consistent with those observed on the Maintenance of Wakefulness Test mean sleep latency score in the primary efficacy analysis.

The analysis is based on a mixed model for repeated measures using the modified intent-to-treat population.

Dose	Treatment Group (N)	Change from Baseline (SE)	Difference from Placebo [95% CI]	p-value
6 g (Week 3)	FT218 (93)	-3.48 (0.42)	-2.06 [-3.23;-0.89]	<0.001
	Placebo (91)	-1.42 (0.42)	-	-
7.5 g (Week 8)	FT218 (83)	-5.34 (0.54)	-3.16 [-4.67;-1.64]	<0.001
	Placebo (85)	-2.18 (0.54)	-	-
9 g (Week 13)	FT218 (73)	-6.52 (0.58)	-3.86 [-5.47;-2.26]	<0.001
	Placebo (80)	-2.66 (0.57)	-	-

Mean (SD) Epworth Sleepiness Scale at Baseline was 16.6 (3.84) in the FT218 group and 17.5 (4.05) in the placebo group.

8.2.6.2.3 Number Of Arousals

The results of the applicant's analysis of the number of arousals (as determined by polysomnography) are displayed in the following applicant table, which is self-explanatory. They indicate an effect of FT218 over placebo on this instrument at a nominally statistically significant level at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day).

The analysis is based on a mixed model for repeated measures using the modified intent-to-treat population.

Table 23 Number of Arousals by PSG: Change from Baseline to the End of Each Treatment Period (MMRM Analysis, 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	81.8 (43.68)	—	—	—	—
Placebo	93	77.2 (38.13)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	88	−31.8 (34.62)	−31.3 (3.45)	−11.29	−20.89, −1.69	0.021
Placebo	88	−17.9 (37.50)	−20.0 (3.44)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	76	−40.6 (45.57)	−39.2 (3.83)	−19.41	−30.00, −8.82	< 0.001
Placebo	79	−19.4 (40.66)	−19.8 (3.76)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	69	−39.4 (39.95)	−39.4 (4.15)	−23.68	−35.01, −12.35	< 0.001
Placebo	78	−15.1 (47.20)	−15.7 (3.96)	—	—	—

Source: Tables 14.2.6.1, 14.2.6.2, 14.2.6.3, and 14.2.6.4
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; PSG = polysomnography; SD = standard deviation; SE = standard error
[1] P-values estimated using an MMRM with change from baseline of number of arousals after sleep onset as the response variable, fixed effects of treatment, visit, treatment by visit, site (United States or Non-United States), covariate of baseline number of arousals after sleep onset, subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were ≤ 0.022.
Note: Arousals are the number of transient arousals on the nocturnal PSG as defined by the American Academy of Sleep Medicine Scoring Guidelines for PSG (Berry 2015).

8.2.6.2.4 Visual Analog Scale Measurement Of Sleep Quality And Refreshing Nature Of Sleep

Visual analog scales measuring both sleep quality and the refreshing nature of sleep were included in the Sleep and Symptom Daily Diary maintained by individual patients.

The results of the applicant's analysis of these outcomes are summarized below.

8.2.6.2.4.1 Visual Analog Scale: Sleep Quality

The following table summarizes the applicant's analysis of sleep quality as measured by the visual analog scale.

The analysis indicates an effect of FT218 over placebo on this instrument at a nominally statistically significant level at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day).

The analysis is based on a mixed model for repeated measures using the modified intent-to-treat population.

Table 24 VAS of Sleep Quality: Change from Baseline to the End of Each Treatment Period (MMRM Analysis, 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[2]						
FT218	97	53.8 (20.85)	—	—	—	—
Placebo	93	55.9 (22.62)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	97	12.3 (13.24)	11.9 (1.11)	6.95	3.84, 10.06	< 0.001
Placebo	93	4.93 (9.17)	4.99 (1.12)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	83	18.9 (17.00)	18.8 (1.40)	9.87	5.98, 13.76	< 0.001
Placebo	85	8.4 (11.47)	9.0 (1.39)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	73	22.3 (18.8)	21.4 (1.66)	10.41	5.82, 15.01	< 0.001
Placebo	79	9.9 (13.77)	11.0 (1.63)	—	—	—

Source: Tables 14.2.7.1, 14.2.7.2, 14.2.7.3, and 14.2.7.4
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; SD = standard deviation; SE = standard error; SSDD = Sleep Symptom Daily Diary; VAS = visual analog scale
[1] P-values were estimated using an MMRM, with change from baseline as the response variable, fixed effects of treatment, visit, treatment by visit, site (US or Non-US), covariate of baseline VAS score, subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were < 0.001.
[2] Baseline was calculated as the mean of the past 14 days preceding Visit 2.
Note: The VAS was part of the SSDD, with a 1 to 100 scale, with 1 indicating "did not sleep" and 100 indicating "slept very well". The VAS is the mean of the responses to the quality of sleep questions averaged over the past 14 days preceding the test day. If a week had < 3 days of SSDD entries, data collected that week (both the score and count of days) were considered invalid and excluded from analyses.

8.2.6.2.4.2 Visual Analog Scale: Refreshing Nature Of Sleep

The following table summarizes the applicant's analysis of the refreshing nature of sleep as measured by the visual analog scale referred to above.

The analysis is consistent with an effect of FT218 over placebo on this instrument at a nominally statistically significant level at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day).

Table 25 VAS of the Refreshing Nature of Sleep: Change from Baseline to the End of Each Treatment Period (MMRM Analysis, 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[2]						
FT218	97	46.5 (21.8)	—	—	—	—
Placebo	93	49.9 (23.3)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	97	13.5 (13.9)	13.0 (1.23)	6.26	2.81, 9.72	< 0.001
Placebo	93	6.6 (10.57)	6.7 (1.25)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	83	20.8 (17.27)	20.6 (1.56)	11.30	6.88, 15.72	< 0.001
Placebo	85	8.9 (14.41)	9.3 (1.58)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	73	24.4 (20.42)	23.8 (1.86)	11.45	6.28, 16.62	< 0.001
Placebo	79	11.5 (15.90)	12.4 (1.84)	—	—	—

Source: Tables 14.2.8.1, 14.2.8.2, 14.2.8.3, and 14.2.8.4
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; SD = standard deviation; SE = standard error; SSDD = Sleep Symptom Daily Diary; VAS = visual analog scale
[1] P-values were estimated using an MMRM, with change from baseline as the response variable, fixed effects of treatment, visit, treatment by visit, site (US or Non-US), covariate of baseline VAS score, subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were < 0.001.
[2] Baseline was calculated as the mean of the past 14 days preceding Visit 2.
Note: The VAS was part of the SSDD, with a 1 to 100 scale, with 1 indicating "not refreshed" and 100 indicating "refreshed". The VAS is the mean of the responses to the refreshing nature of sleep questions averaged over the past 14 days preceding the test day. If a week had < 3 days of SSDD entries, data collected that week (both the score and count of days) were considered invalid and excluded from analyses.

8.2.6.2.5 Number Of Hypnagogic Hallucinations

The following table summarizes the applicant's analysis of the number of hypnagogic hallucinations derived from the Sleep and Symptom Daily Diary maintained by individual patients.

The analysis did not indicate an effect of any dose of FT218 on this outcome.

Table 26 Number of Hypnogogic Hallucinations: Change from Baseline to the End of Each Treatment Period (MMRM Analysis, NT1 Subjects in the 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[2]						
FT218	73	0.45 (0.40)	—	—	—	—
Placebo	72	0.52 (0.41)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	73	−0.12 (0.18)	−0.12 (0.02)	−0.014	−0.076, 0.049	0.664
Placebo	72	−0.11 (0.21)	−0.11 (0.02)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	62	−0.21 (0.29)	−0.21 (0.03)	−0.079	−0.166, 0.007	0.073
Placebo	65	−0.14 (0.26)	−0.13 (0.03)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	54	−0.22 (0.32)	−0.23 (0.04)	−0.065	−0.168, 0.039	0.217
Placebo	62	−0.19 (0.32)	−0.17 (0.04)	—	—	—

Source: Tables 14.2.9.1, 14.2.9.2, 14.2.9.3, and 14.2.9.4
Abbreviations: CI = confidence interval; HH = hypnogogic hallucinations; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; NT1 = type 1 narcolepsy; SD = standard deviation; SE = standard error; SSDD = Sleep Symptom Daily Diary
[1] P-values were estimated using an MMRM with change from baseline (or its log transformation) as the response variable, fixed effects of treatment, visit, treatment by visit, site (US or Non-US), covariate of baseline number of HH (or the log transformation of baseline), subjects as random effect, and unstructured variance-covariance structure. None of the sensitivity analysis randomization tests reached statistical significance.
[2] Baseline was calculated as the mean of the past 14 days preceding Visit 2.
Note: The number of HH was collected via the SSDD. Averaged quantity of HH and/or their log transformed data (whichever gave minimal Akaike's Information Criterion) were used in the MMRM analysis. Averaged quantity was calculated as the number of events averaged over the 14 days preceding the test day. If a week had < 3 days of SSDD entries, data collected that week (both the score and count of days) were considered invalid and excluded from analyses.

8.2.6.2.6 Number Of Sleep Paralysis Events

The following table summarizes the applicant's analysis of the number of sleep paralysis events as derived from the Sleep and Symptom Daily Diary maintained by individual patients.

The effects seen at all three doses of FT218 in this study were only nominally statistically significant.

Table 27 Number of Sleep Paralysis Events: Change from Baseline to the End of Each Treatment Period (MMRM Analysis, NT1 Subjects in the 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[2]						
FT218	73	0.67 (0.95)	—	—	—	—
Placebo	72	0.94 (1.38)	—	—	—	—
Change to Visit 4 (Week 3)						
6.0 g FT218	73	−0.24 (0.61)	−0.28 (0.06)	−0.190	−0.370, −0.010	0.039
Placebo	72	−0.12 (0.56)	−0.09 (0.06)	—	—	—
Change to Visit 6 (Week 8)						
7.5 g FT218	62	−0.42 (0.71)	−0.42 (0.07)	−0.224	−0.412, −0.035	0.021
Placebo	65	−0.24 (0.61)	−0.20 (0.07)	—	—	—
Change to Visit 8 (Week 13)						
9.0 g FT218	54	−0.39 (0.80)	−0.43 (0.08)	−0.234	−0.453, −0.014	0.037
Placebo	62	−0.21 (0.62)	−0.19 (0.08)	—	—	—

Source: Tables 14.2.10.1, 14.2.10.2, 14.2.10.3, and 14.2.10.4
Abbreviations: CI = confidence interval; MMRM = mixed effect model for repeated measures; mITT = modified intent-to-treat; NT1 = type 1 narcolepsy; SD = standard deviation; SE = standard error; SP = sleep paralysis; SSDD = Sleep Symptom Daily Diary
[1] P-values were estimated using an MMRM with change from baseline as the response variable, fixed effects of treatment, visit, treatment by visit, site (United States or Non-United States), covariate of baseline number of SP, and subjects as random effect, and unstructured variance-covariance structure. All sensitivity analysis randomization test p-values were ≤ 0.042.
[2] Baseline was calculated as the mean of the past 14 days preceding Visit 2.
Note: The number of SP events was collected via the SSDD. Averaged quantity of SP events was used in this summary, calculated as the number of events averaged over the 14 days preceding the test day. If a week had< 3 days of SSDD entries, data collected of that week (both the score and count of days) were considered invalid and excluded from analyses.

8.2.7 Safety Results

8.2.7.1 Extent Of Exposure

Exposure overall and by treatment period is summarized in the following table which I have copied from this application. As the table indicates, mean exposure in the FT218 and placebo groups.

Table 28 Exposure to Study Drug (Safety Population)

Exposure (days)	FT218 N = 107	Placebo N = 105	Total N = 212
Overall treatment period, n	107	105	212
Mean (SD)	72.1 (30.55)	76.0 (27.84)	74.0 (29.24)
Period 3a, 6.0 g FT218 or placebo, n	97	102	199
Mean (SD)	13.8 (1.05)	13.8 (1.22)	13.8 (1.14)
Period 3b (i and ii) 7.5 g FT218 or placebo, n	88	88	176
Mean (SD)	33.2 (6.55)	34.0 (3.84)	33.6 (5.36)
Period 3c (i and ii), 9.0 g FT218 or placebo, n	77	80	157
Mean (SD)	33.6 (5.08)	34.6 (1.73)	34.1 (3.78)

Source: Table 14.1.5
Abbreviations: SD = standard deviation
Note: Treatment exposure = last dose date – first dose date + 1.

8.2.7.2 Adverse Events

8.2.7.2.1 All Treatment-Emergent Adverse Events

Treatment-emergent adverse events were recorded from the time of signing of the informed consent form until 7 days after the last dose of study medication.

During this study, 83 subjects (77.6%) of patients who received at least one dose of FT218 experienced at least one adverse event compared with at least 49 subjects (46.7%) who received at least one dose of placebo.

Adverse events (based on Preferred Terms) that occurred in ≥ 5% of all subjects who received FT218 (at any dose) and at rates higher than placebo were as follows: nausea (22.4%), headache (18.7%), vomiting (17.8%), dizziness (15.9%), decreased appetite (12.1%), anxiety (7.5%), hyperhidrosis (5.6%), and weight decreased (5.6%).

Adverse events (based on Preferred Terms) that occurred in ≥ 5% of all subjects who received FT218 (at the 9 g/day dose) and at rates higher than placebo were as follows: enuresis (9.1%), vomiting (9.1%), dizziness (5.2%), and weight decreased (5.2%).

Treatment-emergent adverse events reported in ≥ 2% of FT218-treated subjects (at all doses and during individual dosing periods) are summarized in the next applicant table.

Preferred term	FT218 dosing period				Overall	
	4.5 g FT218 N = 107	6.0 g FT218 N = 97	7.5 g FT218 N = 88	9.0 g FT218 N = 77	FT218 N = 107	Placebo N = 105
Any TEAE	37 (34.6)	38 (39.2)	42 (47.7)	43 (55.8)	83 (77.6)	49 (46.7)
Nausea	8 (7.5)	9 (9.3)	7 (8.0)	3 (3.9)	24 (22.4)	4 (3.8)
Headache	8 (7.5)	5 (5.2)	6 (6.8)	3 (3.9)	20 (18.7)	12 (11.4)
Vomiting	4 (3.7)	5 (5.2)	7 (8.0)	7 (9.1)	19 (17.8)	4 (3.8)
Dizziness	6 (5.6)	4 (4.1)	5 (5.7)	4 (5.2)	17 (15.9)	0
Enuresis	2 (1.9)	4 (4.1)	8 (9.1)	7 (9.1)	17 (15.9)	0
Decreased appetite	4 (3.7)	4 (4.1)	3 (3.4)	3 (3.9)	13 (12.1)	0
Anxiety	3 (2.8)	0	4 (4.5)	1 (1.3)	8 (7.5)	3 (2.9)
Hyperhidrosis	2 (1.9)	2 (2.1)	1 (1.1)	1 (1.3)	6 (5.6)	0
Nasopharyngitis	0	2 (2.1)	3 (3.4)	2 (2.6)	6 (5.6)	7 (6.7)
Weight decreased	1 (0.9)	1 (1.0)	0	4 (5.2)	6 (5.6)	1 (1.0)
Abnormal dreams	1 (0.9)	1 (1.0)	2 (2.3)	1 (1.3)	5 (4.7)	0
Somnolence	0	1 (1.0)	2 (2.3)	3 (3.9)	5 (4.7)	1 (1.0)
Arthralgia	1 (0.9)	0	1 (1.1)	2 (2.6)	4 (3.7)	2 (1.9)
Asthenia	1 (0.9)	1 (1.0)	2 (2.3)	0	4 (3.7)	1 (1.0)
Diarrhoea	1 (0.9)	1 (1.0)	1 (1.1)	1 (1.3)	4 (3.7)	0
Dry mouth	1 (0.9)	1 (1.0)	1 (1.1)	1 (1.3)	4 (3.7)	2 (1.9)
Dyspnoea	0	3 (3.1)	0	1 (1.3)	4 (3.7)	0
Pain in extremity	0	1 (1.0)	1 (1.1)	2 (2.6)	4 (3.7)	2 (1.9)
Paraesthesia	1 (0.9)	2 (2.1)	0	1 (1.3)	4 (3.7)	0
Cough	0	1 (1.0)	1 (1.1)	1 (1.3)	3 (2.8)	4 (3.8)
Depression	0	1 (1.0)	1 (1.1)	1 (1.3)	3 (2.8)	1 (1.0)
Fatigue	2 (1.9)	0	1 (1.1)	0	3 (2.8)	1 (1.0)
Hypoaesthesia	1 (0.9)	2 (2.1)	0	0	3 (2.8)	0
Pain	1 (0.9)	0	1 (1.1)	1 (1.3)	3 (2.8)	0
Pyrexia	1 (0.9)	0	2 (2.3)	0	3 (2.8)	3 (2.9)
Seasonal allergy	0	1 (1.0)	0	2 (2.6)	3 (2.8)	0
Sleep paralysis	0	0	2 (2.3)	1 (1.3)	3 (2.8)	0
Somnambulism	1 (0.9)	2 (2.1)	0	0	3 (2.8)	0
Tremor	1 (0.9)	1 (1.0)	1 (1.1)	1 (1.3)	3 (2.8)	0
Upper respiratory tract infection	0	1 (1.0)	1 (1.1)	1 (1.3)	3 (2.8)	2 (1.9)

Source: Tables 14.3.1.2.1, 14.3.1.2.2, 14.3.1.2.3, 14.3.1.2.4, and 14.3.1.2.5
Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event;
Note: TEAEs during each FT218/placebo treatment period were defined as an AE occurring or increasing in severity on or after the first dose of the respective treatment period and before the last dose. If a subject experienced more than one AE in a category, the subject was counted only once in that category for that treatment period and in the overall total.

Severe treatment-emergent adverse events were observed in 11 subjects treated with FT218 and in 5 subjects treated with placebo. The remaining treatment-emergent adverse events were judged to be mild or moderate in their severity. Severe treatment-emergent adverse events are listed in the following table which is self-explanatory.

Subject number Age/Sex	Preferred term	Dosing period at onset	SAE Yes/No	Action taken	Outcome	Study drug relationship
FT218-treated subjects						
(b) (6) 48/female	Paraesthesia	6.0 g	Yes	Drug interrupted	Resolved	Unlikely
(b) (6) 32/male	Liver function tests increased	9.0 g	No	Discontinued supplements	Resolved	Not related
	Weight decreased	9.0 g	No	Dose not changed	Resolved	Related
(b) (6) 30/female	Weight decreased	4.5 g	No	Drug interrupted	Resolved	Related
	Decreased appetite	7.5 g	No	Drug interrupted	Resolved	Related
	Anxiety	7.5 g	No	Drug withdrawn	Resolved	Related
	Obsessive thoughts	7.5 g	No	Drug interrupted	Resolved	Related
(b) (6) 25/female	Diabetes mellitus inadequate control	4.5 g	Yes	Drug withdrawn	Resolved	Not related

Subject number Age/Sex	Preferred term	Dosing period at onset	SAE Yes/No	Action taken	Outcome	Study drug relationship
(b) (6) 37/female	Anxiety	7.5 g	No	Concomitant medication	Resolved	Related
	Suicidal ideation	9.0 g	Yes	Drug withdrawn	Resolved	Related
(b) (6) 18/male	Headache	7.5 g	No	Dose not changed	Resolved	Not related
(b) (6) 22/female	Dizziness	4.5 g	No	Dose not changed	Resolved	Related
	Headache	4.5 g	No	Dose not changed	Resolved	Related
(b) (6) 49/female	Nausea	7.5 g	No	Drug withdrawn	Resolved	Related
	Dizziness	7.5 g	No	Drug withdrawn	Resolved	Related
	Headache	7.5 g	No	Drug withdrawn	Resolved	Related
	Depression	7.5 g	No	Drug withdrawn	Resolved	Related
(b) (6) 36/female	Perirectal abscess	7.5 g	Yes	Drug withdrawn	Resolved	Not related
(b) (6) 22/female	Abortion induced	6.0 g	No	Drug withdrawn	Resolved	Not related
(b) (6) 48/female	Sudden onset of sleep	4.5 g	No	Dose not changed	Resolved	Related
Placebo-treated subjects						
(b) (6) 40/male	Essential hypertension	7.5 g	No	Drug interrupted	Resolved	Possibly
(b) (6) 23/female	Somnolence	4.5 g	No	Provided alternate transportation	Resolved	Related
(b) (6) 40/female	Dental caries	4.5 g	No	Restoration of gum	Resolved	Not related
	Drug hypersensitivity	4.5 g	Yes	Drug withdrawn	Resolved	Not related
	Tooth infection	4.5 g	No	Concomitant medication	Resolved	Not related
	Tooth fracture	4.5 g	No	Root extraction	Resolved	Not related
	Tooth fracture	4.5 g	No	Concomitant medication	Resolved	Not related
(b) (6) 17/female	Anxiety	6.0 g	No	Drug withdrawn	Resolved	Not related
(b) (6) 30/female	Pelvic inflammatory disease	9.0 g	Yes	Concomitant medication	Resolved	Unlikely

8.2.7.2.2 Deaths

There were no deaths during this study.

8.2.7.2.3 Serious Adverse Events

Serious adverse events (all non-fatal) that occurred during this study are summarized in the following applicant table.

Subject number	Age/sex	Onset/Stop date (study day) Onset dose level	Preferred term	Severity	Reason serious[1] Action taken	Outcome Study drug relationship
FT218-treated subjects						
(b) (6)	48/female	14/18 6.0 g	Paraesthesia	Severe	Hospitalization Drug interrupted	Resolved Unlikely
	25/female	4/6 4.5 g	Diabetes mellitus inadequate control	Severe	Hospitalization Drug withdrawn	Resolved Not related
	47/female	97/100 Post-treatment[2]	Hypertension	Mild	Hospitalization Dose not changed	Resolved Unlikely
	37/female	63/66 9.0g	Suicidal ideation	Severe	Hospitalization Drug withdrawn	Resolved Related
	36/female	36/302 7.5 g	Perirectal abscess	Severe	Hospitalization Drug withdrawn	Resolved Not related
Placebo-treated subjects						
(b) (6)	40/female	5/14 4.5 g	Drug hypersensitivity	Severe	Hospitalization Drug withdrawn	Resolved Not related
	30/female	67/92 9.0 g	Pelvic inflammatory disease	Severe	Important medical event Concomitant medication	Resolved Unlikely

I have read the narratives for each serious adverse event outlined in the above table. A more detailed description of any of those events in this review is not warranted.

8.2.7.2.4 Premature Discontinuations Due To Adverse Events

23 subjects (21.5%) in the FT218 group and 3 subjects (2.9%) in the placebo group discontinued treatment prematurely due to adverse events. These events are summarized in the following applicant table.

I have read the narratives for adverse event outlined in the table below. Again, a more detailed description of any of those events in this review is not warranted.

Table 36 Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation (Safety Population)

Subject number Age/sex	Dose period at withdrawal	Onset date/Stop date (study day) Dose period	Preferred term	Severity	Serious Yes/No	Outcome Study drug relationship
FT218-treated subjects						
(b) (6) 27/female	6.0 g	16/28 6.0 g	Depression	Moderate	No	Resolved, Not related
(b) (6) 42/female	6.0 g	8/16 6.0 g	Nausea	Moderate	No	Resolved Related
(b) (6) 27/male	4.5 g	3/3 4.5 g	Dizziness	Mild	No	Resolved Possibly
(b) (6) 30/female 7.5 g	7.5 g	36/59 7.5 g	Anxiety	Severe	No	Resolved Related
(b) (6) 22/female	6.0 g	1/42 4.5 g	Pain	Mild	No	Resolved Not related
		1/42 4.5 g	Peripheral swelling	Mild	No	Resolved Not related
		1/42 4.5 g	Pyrexia	Mild	No	Resolved Not related
		1/42 4.5 g	Skin warm	Mild	No	Resolved Not related
		2/42 4.5 g	Decreased appetite	Mild	No	Resolved Related
		2/42 4.5 g	Headache	Mild	No	Resolved Related
		2/42 4.5 g	Nausea	Mild	No	Resolved Related
		11/11 6.0 g	Enuresis	Mild	No	Resolved Related
		13/13 6.0 g	Dyspnoea	Mild	No	Resolved Not related
(b) (6) 29/female	4.5 g	1/3 4.5 g	Anxiety	Moderate	No	Resolved Related
		1/3 4.5 g	Dizziness	Moderate	No	Resolved Related
(b) (6) 18/female	9.0 g	71/94 9.0 g	Nausea	Moderate	No	Resolved Not related
		71/94 9.0 g	Vomiting	Moderate	No	Resolved Not related
(b) (6) 17/female	4.5 g	2/2 4.5 g	Painful respiration	Mild	No	Resolved Possibly related
(b) (6) 34/female	7.5 g	24/24 7.5 g	Diarrhoea	Moderate	No	Resolved Related

Subject number Age/sex	Dose period at withdrawal	Onset date/Stop date (study day) Dose period	Preferred term	Severity	Serious Yes/No	Outcome Study drug relationship
		24/24 7.5 g	Vomiting	Moderate	No	Resolved Related
(b) (6) 27/female	9.0 g	60/96 9.0 g	Dyspnoea	Moderate	No	Resolved Related
(b) (6) 33/female	9.0 g	82/104 9.0 g	Pregnancy	Not reported	No	Resolved Not related
(b) (6) 45/female	4.5 g	4/5 4.5 g	Dysphagia	Moderate	No	Resolved Possibly related
(b) (6) 26/female	4.5 g	1/10 4.5 g	Anxiety	Moderate	No	Resolved Possibly related
(b) (6) 25/female	4.5 g	4/6 4.5 g	Diabetes mellitus inadequate control	Severe	Yes	Resolved Not related
(b) (6) 37/female	9.0 g	63/66 9.0 g	Suicidal ideation	Severe	Yes	Resolved Related
(b) (6) 37/female	6.0 g	14/ongoing 6.0 g	Somnolence	Mild	No	Ongoing Possibly related
		14/ongoing 6.0 g	Abnormal dreams	Mild	No	Ongoing Possibly
(b) (6) 25/female	9.0 g	58/63 9.0 g	Dizziness	Moderate	No	Resolved Related
(b) (6) 49/female	7.5 g	23/27 7.5 g	Nausea	Severe	No	Resolved Related
		23/27 7.5 g	Dizziness	Severe	No	Resolved Related
		23/27 7.5 g	Headache	Severe	No	Resolved Related
		23/28 7.5 g	Depression	Severe	No	Resolved Related
(b) (6) 36/female	7.5 g	36/302 7.5 g	Perirectal abscess	Severe	Yes	Resolved Not related
(b) (6) 22/female	6.0 g	20/25 6.0 g	Pregnancy	Not reported	No	Resolved Not related
		24/25 6.0 g	Abortion induced	Severe	No	Resolved Not related
(b) (6) 48/female	7.5 g	38/63 7.5 g	Depressed mood	Moderate	No	Resolved Possibly elated
(b) (6) 35/female	6.0 g	9/23 6.0 g	Nausea	Mild	No	Resolved Related
		9/23 6.0 g	Dizziness	Mild	No	Resolved Related
		9/23 6.0 g	Headache	Mild	No	Resolved Related
		9/23 6.0 g	Restlessness	Mild	No	Resolved Possibly related

Subject number Age/sex	Dose period at withdrawal	Onset date/Stop date (study day) Dose period	Preferred term	Severity	Serious Yes/No	Outcome Study drug relationship
(b) (6) 48/female	4.5 g	6/9 4.5 g	Delirium	Moderate	No	Resolved Related
Placebo-treated subjects						
(b) (6) 40/female	4.5 g	5/14 4.5 g	Drug hypersensitivity	Severe	Yes	Resolved Not related
(b) (6) 49/male	7.5 g	22/79 7.5 g	Sleep apnoea syndrome	Mild	No	Resolved Possibly related
(b) (6) 17/female	6.0 g	8/16 6.0 g	Nausea	Moderate	No	Resolved Related
		9/13 6.0 g	Anxiety	Severe	No	Resolved Not related
		9/16 6.0 g	Vomiting	Moderate	No	Resolved Related

8.2.7.2.5 Adverse Events Of Special Interest

The following were considered adverse events of special interest: respiratory depression, major depression, sleep apnea, suicide attempt, suicidal ideation, euphoric mood, psychosis, paranoia, hallucination, abnormal thinking, agitation, convulsion or epilepsy, abuse and dependence, withdrawal syndrome, and rebound effects.

Study sites also separately reported medication errors as adverse events of special interest.

Adverse events of special interest other than medication errors are summarized in the following table, which I have copied from the submission.

Table 37 Summary of Adverse Events of Special Interest Other than Medication Errors (Safety Population)

Subject number	Age/sex	Onset/Stop date (study day) Dose period at onset	Preferred term	Severity	Serious Yes/No	Outcome Study drug relationship
FT218-treated subjects						
(b) (6)	37/Female	63/66 9.0 g	Suicidal ideation	Severe	Yes	Resolved Related
	47/Male	91/92 9.0 g	Sleep apnea syndrome	Moderate	No	Resolved Possibly related
Placebo-treated subjects[1]						
(b) (6)	44/Male	10/10 6.0 g	Suicidal ideation	Mild	No	Resolved Not related
	28/Female	3/280 4.5 g	Agitation	Mild	No	Resolved Unlikely

Source: Listing 16.2.7.5
[1] Does not include one subject in the placebo group who discontinued due to an AE of worsening sleep apnea.

Adverse events of special interest that were medication errors are reported in the next table.

Table 38 Summary of Adverse Events of Special Interest with a Preferred Term of Medication Error (Safety Population)

Subject number	Age/sex	Onset/Stop date (study day) Dose period at onset	Preferred term	Description	Severity	Serious Yes/No	Outcome Study drug relationship
FT218-treated subjects							
(b) (6)	24/Female	8/21 6.0 g	Medication error	The subject took one sachet/night (3.0 g dose) Weeks 6 to 7 for the 6.0g FT218 dosing period	Mild	No	Resolved Not related
	26/Female	2/3 4.5 g	Medication error	The subject took the second dose of study drug after adding the powder to gelatin capsules	Mild	No	Resolved Not related
	27/Female	1/2 4.5 g	Medication error	The subject inadvertently took 2 x 4.5g sachets during Week 1 (9.0 g total dose) due to misunderstanding the dosing instructions	Mild	No	Resolved Not related
	26/Male	8/21 6.0 g	Medication error	The subject took half of the prescribed dose for Weeks 2 to 3 (total dose of 3.0 g instead of 6.0 g)	Mild	No	Resolved Not related
	23/Male	10/10 6.0 g	Medication error[1]	Per the AESI report, the subject got out of bed after taking the study drug to use the bathroom (which was downstairs) and subsequently had a fall on the stairs	Mild	No	Resolved Related
	18/Female	76/78 9.0 g	Medication error	Per the AESI report, the subject thought the full dose was 1 sachet, and inadvertently took only 1 sachet/night (4.5 g) instead of 2 sachets/night (9.0 g) on two occasions during the 9.0 g treatment period	Mild	No	Resolved Not related
Placebo-treated subjects							
(b) (6)	26/Male	8/20 6.0 g	Medication error	The subject took 1 x 3.0 g/night Weeks 2 to 3 (total dose of 3.0 g instead of 6.0 g)	Mild	No	Resolved Not related

Source: Listing 16.2.7.1, 16.2.7.5, 16.2.3, and data on file with the sponsor.
[1] The fall was reported as an AE. The principal investigator also reported this event as a medication error. Although the subject took the medication correctly, the subject did not follow the instructions to remain in bed after taking study drug, which was considered by the investigator to be a medication error.

I have read the narratives for all the adverse events reported above. They do not warrant further description in this review.

8.2.7.3 Safety Laboratory Tests

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

8.2.7.4 Vital Signs

The changes observed in systolic and diastolic blood pressure, and in heart rate during this study were unremarkable and did not appear to be of clinical significance.

8.2.7.5 Body Weight

The applicant has presented an analysis of changes in body weight across the course of the study. There were no findings of concern in these analyses.

8.2.7.6 Electrocardiogram

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

8.2.7.7 Columbia-Suicide Severity Rating Scale

A total of 4 subjects answered "yes" to one or more suicidal ideation-related questions of the Columbia-Suicide Severity Rating Scale during the study: 3 of these subjects (2.8%) received FT218 and 1 subject (1.0%) received placebo. 1 subject treated with FT218 discontinued study medication on account of suicidal ideation.

No subject answered "yes" to any of the suicidal behavior-related questions of the Columbia-Suicide Severity Rating Scale during the study.

8.2.7.8 Pregnancies

Two subjects in the FT218 group became pregnant during the study; both were withdrawn from the study and later underwent abortions.

8.3 Applicant's Conclusions

The applicant has made the following conclusions (among others) based on the data for this study.

- FT218 was highly effective in the treatment of narcolepsy across the three primary efficacy endpoints.

- The adverse events seen with FT218 were consistent with what was to be expected for sodium oxybate.

- FT218 has a favorable risk-benefit profile for the treatment of narcolepsy.

8.4 Reviewer's Summary Comments

8.4.1 Study Design

The main features of the design of Study CLFT218-1501 were as follows.

- The primary objective of that study was to demonstrate the efficacy of FT218 in doses of 6.0 g, 7.5 g, and 9.0 g nightly in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

- This was to be a randomized, double-blind, placebo-controlled, parallel-arm study.

- Two populations of patients with narcolepsy (men and women; age ≥ 16 years) were to be studied: patients with excessive daytime sleepiness and cataplexy (Type 1 narcolepsy); and patients with excessive daytime sleepiness and no cataplexy (Type 2 narcolepsy). Criteria for a diagnosis of narcolepsy with or without cataplexy were to be based on the following, (and were also to meet the International Classification of Sleep Disorders-3 criteria for NT1 or NT2): the results of on overnight polysomnogram and next-day Multiple Sleep Latency test with two or more sleep-onset rapid eye movement periods and with mean sleep latency in the pathological range of < 8 minutes; and excessive daytime sleepiness for at least 3 months currently presenting with an Epworth Sleepiness Scale score > 10.

- Concomitant stimulant use was to be permitted, although not required, if the stimulant dose had been stable for at least 3 weeks at screening. Patients enrolled should have been naïve to Xyrem®.

- 264 patients were to be enrolled in the study and randomized to 2 treatment arms in equal proportions (i.e., 132 patients per treatment arm): Arm 1 consisting of FT218 in a single dose of 9.0 g nightly (final dose, reached by forced dose titration beginning with a dose of 4.5 g nightly); and Arm 2 consisting of placebo administered nightly. Randomization was to be stratified according to narcolepsy type (i.e., Type 1 or Type 2). A minimum of 107 patients per treatment arm was to have Type 1 narcolepsy.

- The study was to have 9 consecutive periods be subsumed under a 3-week screening period, a 13-week treatment period, and a 1-week follow-up period.

- The primary efficacy measures were the following: Maintenance of Wakefulness score and Clinical Global Impression for excessive daytime sleepiness; and mean number of cataplexy attacks over a 2-week period. Secondary efficacy measures were to be as follows: two measures derived from polysomnography to be used as measures of disturbed nocturnal sleep; Epworth Sleepiness Scale score; number of transient nocturnal arousals (based on polysomnography); quality of sleep as measured by a visual analog scale; number of hypnagogic hallucinations as recorded in a patient-maintained diary; and the number of sleep paralysis events as recorded in a patient-maintained diary. Safety measures were to include adverse events, vital signs, safety laboratory tests, electrocardiogram, and physical examinations.

- A complex plan for sequential hypothesis testing of the primary efficacy measures was described. Hypothesis testing was to occur, comparing each dose of FT218 with placebo in descending order (i.e., FT218 9 g/day vs placebo, then FT 7.5 g/day vs placebo, and finally FT218 6 g/day vs. placebo). At each dose level, the effect of FT218 was to be compared with that of placebo first on the Maintenance of Wakefulness Test mean sleep latency score and Clinical Global Impression of Change, and then on the change from baseline to endpoint in daily cataplexy score. Each hypothesis test was to be performed at a significance level of 0.05 (two-sided). Rejection of the study hypothesis at any step was to terminate all further steps of the testing sequence. Methods of analysis were also specified for the secondary efficacy measures.

8.4.2 Study Results

This study was conducted according to its final protocol.

413 patients were enrolled in the study. 222 patients were randomized with at least 111 patients being assigned to each treatment group. 212 patients (107 patients in the FT218 group and 105 patients in the placebo group) received at least one dose of study medication. 148 subjects (69.8% of those randomized) completed the study: 69 patients in the FT218 treatment group and 79 patients in the placebo group.

The treatment groups were comparable on each of the 3 primary efficacy parameters at baseline. The primary efficacy analysis (conducted in the modified intent-to-treat population) indicated that FT218 demonstrated a statistically significant superiority over placebo ($p < 0.0001$) on all three primary efficacy parameters, the Maintenance of Wakefulness Test mean sleep latency, the Clinical Global Impression of Sleepiness, and the mean weekly number of cataplexy attacks; this effect was apparent at all 3 doses of FT218 (6.0 g/day, 7.5 g/day, and 9.0 g/day). At the 9.0 g/day dose: the least squares mean difference in the change from baseline to Week 13 in mean sleep latency on the Maintenance of Wakefulness Test was 6.13 minutes; the observed mean

difference in the Clinical Global Impression of Sleepiness at Week 9 was 1.0 point (with 72% of those randomized to FT218 and 31.6% of those randomized to placebo being much improved or very much improved); and the least squares mean difference in the weekly number of cataplexy attacks was -6.65.

The adverse event profile for FT218, as seen in this study was not significantly different from that of other oxybate products and did not raise any special concerns. The other safety outcomes did not reveal any data of concern.

9. 120-Day Safety Update: Study CLFT218-1901

The data included in the 120-Day Safety Update are entirely from Study CLFT218-1901.

CLFT218-1901 is an open-label study that was still ongoing when the 120-Day Safety Update was submitted on April 13, 2021.

Although that study was also ongoing at the time this NDA was initially submitted on December 15, 2020, no safety data for CLFT218-1901 were included in that submission by prior agreement with the Agency. Instead, all that the same submission contained for Study CLFT218-1901 was a detailed description of the design of that study.

A summary description of the design of Study CLFT218-1901 together with the main safety data for that study are below.

9.1 Outline Of Study Protocol

Version 2.0 of Protocol CLFT218-1901, dated July 31, 2020, is summarized below.

9.1.1 Title

An Open-Label Study To Evaluate Long-Term Safety And Tolerability Of A Once-Nightly Formulation Of Sodium Oxybate Extended-Release For Oral Suspension (FT218) And The Ability To Switch From Twice-Nightly Immediate-Release Sodium Oxybate To Once-Nightly FT218 For the Treatment Of Excessive Daytime Sleepiness And Cataplexy In Subjects With Narcolepsy.

9.1.2 Objectives

9.1.2.1 Primary (Safety) Objectives

To evaluate the long-term safety and tolerability of FT218

9.1.2.2 Secondary Objectives

To evaluate:

- The long-term efficacy of FT218.
- The dosing and tolerability in switching from twice-nightly sodium oxybate immediate release to FT218.
- The safety of switching from twice-nightly sodium oxybate immediate-release to FT218.
- The preferred dosing regimen for FT218.

9.1.3 Design, Dose, Sample Size, And Duration

This was to be an open-label uncontrolled study of 24 months duration.

Subjects to be enrolled in this study were to consist of patients with either Type 1 or Type 2 narcolepsy and were to be in 2 groups.

- Group A consisting of subjects who completed Study CLFT218-1501.
- Group B consisting of subjects who were currently receiving twice-nightly sodium oxybate.

The study was to have 3 consecutive periods.

- Period 1, a dose-titration period lasting 1-2 months.
- Period 2, a stable-dose period lasting up to 24 months.
- Period 3, a follow-up period lasting 1 week.

The study design is depicted graphically in the applicant schematic below.

The two study groups were each expected to contain the following number of subjects.

Group A: 100 subjects.
Group B: 150 subjects.

The dosing regimen for each group during Study Period 1 is summarized as follows.

- For Group A, dosing with FT218 once nightly was to begin at a dose of 4.5 g nightly, with weekly increments by 1.5 g nightly until the highest tolerated dose up to a maximum of 9.0 g nightly was reached or the dose deemed effective by the investigator was reached (titration up or down was permitted). In addition, the investigator had flexibility to adjust the dose over a longer period if necessary.

- For Group B, dosing with FT218 once nightly was to begin at a dose equivalent or closest to the total gram dose of twice-nightly sodium oxybate. That dose was then to be titrated up or down in accordance with safety, tolerability, and effectiveness as determined by the investigator. Dose titration up or down was to be permitted during the dose titration period.

Other aspects of the dose titration regimen for the two treatment groups are further described in this submission.

9.1.4 Key Inclusion Criteria

The inclusion criteria for this study are copied below from the submission. The inclusion criteria are self-explanatory.

1. Subjects who:
    a. Are receiving a stable doses of twice-nightly sodium oxybate IR for at least 4 weeks and are willing to switch to FT218

       OR

    b. Completed the CLFT218-1501 REST-ON Study in a compliant manner and for whom the Investigator determines would receive benefit from treatment with FT218
2. Subjects16 years of age and older.
3. Subjects have a diagnosis of narcolepsy, either confirmed prior to the REST-ON study or as confirmed by the Investigator for subjects currently on twice-nightly sodium oxybate IR.
4. Willing and able to give written informed consent for study participation; young adults (16 and 17 years old) who have not reached the age of majority must be capable of giving assent in addition to consent from a legally authorized guardian, as required by local laws and regulations.
5. Subjects may use concomitant stimulants, but must comply with the following:
    a. Stable regimen of stimulants for at least 3 weeks prior to entering the study
6. Female subjects who:
    a. Are postmenopausal for at least 1 year before the screening visit or demonstrate follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status in the absence of amenorrhea for 1 year
    b. Are surgically sterile, **OR**
    c. Are of childbearing potential and agree to practice effective method of contraception, from the time of signing the informed consent form through 1 week after the last dose of investigational product
7. Willing and able to comply with all study requirements and procedures for the duration of the clinical study
8. Willing to adhere to all study restrictions including:
    a. Comply with the requirement to remain in bed for a minimum of 6 hours after taking the investigational product
    b. Refrain from operating a car or heavy machinery, if determined necessary by the investigator, or refrain from operating a car or heavy machinery for at least 6 hours after taking the nightly dose of investigational product
    c. Avoid alcohol for the duration of the clinical study
    d. Abstain from cannabis (therapeutic or illicit) and willing to comply with study visit UDS as determined by the PI and/or Sponsor
9. Women of childbearing potential must have a negative serum pregnancy test at V0 and negative urine pregnancy test at each subsequent visit in Period 1 and at each Assessment & Dispensing Visit in Period 2 and at End of Study (EOS).

9.1.5 Key Exclusion Criteria

These are copied below from the submission.

1. Subjects that terminated the CLFT218-1501 REST-ON Study prior to completing Visit 8
2. Any use of the following prohibited medications for the duration of the clinical study:
    a. Anticonvulsants
    b. Clonidine
    c. Hypnotics
    d. Anxiolytics
    e. Sedating antihistamines
    f. Antipsychotics
    g. Other experimental medications designed to treat narcolepsy, cataplexy, or any other condition
    h. Other medications with significant sedating effects/CNS depressant effects
3. Treatment with any investigational products (*other than on the REST-ON study*) within 1 month before study enrollment
4. A diagnosis of sleep apnea where AHI is ≥15 /or requires current use of CPAP or other devices for sleep apnea.
    a. Subjects must have a sleep study (Polysomnography (PSG) or home sleep study) in last two years with AHI <15. Subjects lacking a documented sleep study in the last two years must be evaluated with the Stop-Bang survey; subjects with scores of 3 or higher, must complete an at home sleep study ruling out sleep apnea.
5. Any unstable or clinically significant medical and/or psychiatric disorders as determined by medical or psychiatric history, physical examination, and/or clinical laboratory test which in the opinion of the investigator may put the subject at risk by participation in the study
6. Any current malignancy and/or history of malignancy within the last five years with the exception of squamous or basal cell carcinoma of the skin or in-situ breast or cervical cancer
7. Any history of seizure disorder, significant head trauma as determined by the investigator, or invasive intracranial surgery
8. Current or history of severe chronic obstructive pulmonary disease; subjects with mild to moderate chronic obstructive pulmonary disease assessed as stable by the principal investigator (PI) are eligible.
9. Principal investigator judgement regarding other underlying respiratory and/or other underlying condition that would potentiate risk of respiratory or CNS depression with concomitant use of sodium oxybate
10. Hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection
11. Recent myocardial infarction or coronary revascularization (less than 3 months)

12. Active human immunodeficiency virus infection or acquired immunodeficiency syndrome related illness
13. Known contraindication/allergy/sensitivity/intolerance to the study drug, sodium oxybate, or the inactive ingredients of FT218
14. Atrial fibrillation or an abnormal electrocardiogram (ECG) demonstrating clinically significant abnormality per the Investigator's judgement
15. Uncontrolled hypertension
16. Succinic semi-aldehyde dehydrogenase deficiency
17. Subject has significant current suicidal ideation within one year prior to Screening or any prior history of suicide attempt
18. Any drug or alcohol use that, in the opinion of the investigator would interfere with study subject safety and adherence to study requirements including history of consumption of more than 14 standard alcoholic drinks per week
19. Required commercial or equivalent driving during the study period
20. Female subjects who are lactating or have a positive pregnancy test
21. Females of reproductive potential not willing or able to employ effective methods of birth control/contraception to prevent pregnancy for the duration of the study and for up to 1 week after completing study treatment
22. Clinically significant laboratory abnormalities that would make subject unsuitable for enrollment, as determined by investigator

9.1.6 Concomitant Medications

See Exclusion Criteria above.

9.1.7 Schedule

A detailed schedule for the study is in the table below, which I have copied from the study protocol.

	Screening Period	Period 1: Titration to Stable Dosing Period		Period 2: Year 1 & Year 2 Stable Dosing Period		Period 3: Study Completion Period	
Overarching Weeks	W-4 to Week 0	Week 1 Baseline	Per Individual Subject Pathway	Monthly	Quarterly[1,7]	Week 1 +108 weeks[1]	EOS + 1 Week
Visit Windows			+/- 3 days	+/- 7 days			+/- 3 days
Visit	Visit 0[2]	Visit 1	Up to Four Visits[3]	Dispensing Visit	Assessment & Dispensing Visit[4]	EOS/ET Visit	Follow-Up Visit
Informed consent	X	X[5]					
Inclusion and exclusion criteria	X	X					
Demographics	X	X[5]					
Medical, surgical & psychiatric history	X	X[5]					
Assessment of prior or current drug abuse & dependence	X	X	X		X		
Physical examination	X	X[5]	X[16]		X[16]	X	
Vital signs	X	X	X		X	X	
Weight, height	X	X[5]				X	
Local clinical labs (biochemistry & hematology)[8]	X	X[5]	X[16]		X[16]	X	
Local Serology (HBsAg, anti-HCVAb)	X	X[5]					
Pregnancy test[6]	X	X	X		X	X	
Urinalysis[8]	X	X[5]					
Urine drug screen[7]	X	X[5]	X[16]		X[16]	X[16]	
12-lead ECG	X	X[5]					
STOP-BANG[18]	X						
At-home Sleep Study[19]	X						
ESS[9]		X			X		
Dispense Diary	X		X[10]		X		
Cataplexy and Diary Training	X	X[5]					
Site Reminder Call to Subject to Complete Diary[11]		X	X		X		
Complete Diary[12]		X	X		X		
Subject Preference Questionnaire					X[13]		
Nocturnal AE questionnaire[14]		X					
CGI-I[15]					X	X	X

	Screening Period	Period 1: Titration to Stable Dosing Period		Period 2: Year 1 & Year 2 Stable Dosing Period		Period 3: Study Completion Period	
Overarching Weeks	W-4 to Week 0	Week 1 Baseline	Per Individual Subject Pathway	Monthly	Quarterly[1,7]	Week 1 +108 weeks[1]	EOS 1 We
Visit Windows			+/- 3 days	+/- 7 days			+/- day
Visit	Visit 0[2]	Visit 1	Up to Four Visits[3]	Dispensing Visit	Assessment & Dispensing Visit[4]	EOS/ET Visit	Follo Up Visi
PGI-I[15]					X	X	X
Drug dispensing		X	X	X	X	X	
Drug accountability			X	X	X	X	X
Adverse events		←----------X----------→					
Concomitant medications		←----------X----------→					
Off-study treatment discussion						X	

ET: Early Termination; EOS: End of Study; SF = Short Form

[1] Study duration for two years or until such time that FT218 receives marketing approval and can be obtained commercially or through other market access programs for an individual subject or the program is terminated by the Sponsor.

[2] Group A subjects: Following informed consent, data from their last visit in REST-ON can be used to populate Visit 1 if no more than 30 days have elapsed since REST-ON Visit 8; Visit 0 won't be required in these cases.

[3] Number of visits following Visit 1 in Period 1 will depend upon each subjects' titration schedule. Visits to be completed weekly in accord with up-titrations or as per alternate schedule determined by the investigator.

[4] If a subject must reduce dose in Period 2, the visit schedule will be adjusted based upon the last visit completed for re-titration.

[5] Required at Visit 1 only for Group A subjects whose REST-ON Visit 8 is also their Visit 1.

[6] Local Laboratory for blood and urine testing will be used. Serum pregnancy test for women of childbearing potential to be done at Visit 0. Thereafter Urine pregnancy test to be done at each assessment visit. Local Laboratory will be used.

[7] To be done at Visit 0 and Visit 1. If positive, re-test to be done. PI discretion will determine need for UDS at each study visit.

[8] Local site urine test strip dip-stick evaluation will be done. (Leukocytes, Nitrite, Urobilogen, Protein, pH, Hemoglobin, Specific Gravity, Ketone, Bilirubin, Glucose)

[9] To be completed in clinic. **ESS only for Group A Subjects.**

[10] Diary dispensed at last period 1 visit prior to transitioning to Period 2 visit schedule.

[11] **Group A Subjects Only**: This call will be made to the subject eight to nine days before the next scheduled visit. The purpose of this call is to remind the subject to complete the diary for seven consecutive days in advance of their next scheduled visit. **CATAPLEXY DIARY** only required at the Baseline visit, once stable dosing achieved and every six months in Period 2.

[12] Diary Data with Number Cataplexy Attacks (NCA) and Symptoms will only be done for **Group A Subjects**.

[13] **Group B Subjects Only:** To be completed once and only by subjects switching from twice-nightly sodium oxybate IR to FT218 once subject has had three months of stable dosing with FT218.

[14] **Group B Subjects Only**: To be completed at Visit 1 only. All questions should be answered, even if subject has taken Xyrem® < 3 months.

[15] **Group A:** Assessment for Improvement as compared to baseline at each assessment visit.

[16] If clinically indicated

[17] The first quarterly safety and efficacy assessment clinic visit will occur three months from the date stable dose was achieved and will coincide with the applicable monthly IMP Dispensation visit

[18] STOP-BANG Questionnaire only required for subjects that have not had a sleep study in the past two years

[19] At-home Sleep Study only required for subjects that have not had a sleep study in the past two years and who score a 3 or higher on the STOP-BANG questionnaire

9.1.8 Outcome Measures

9.1.8.1 Safety Measures

Adverse events, vital signs, safety laboratory tests, and physical examinations.

9.1.8.2 Efficacy Measures

Epworth Sleepiness Scale, Clinical Global Impression of Improvement, and Patient Global Impression of Improvement.

9.2 Study Results

The results presented below are based on an interim analysis of safety, apparently dated February 26, 2021.

9.2.1 Subject Disposition

At the time that this safety analysis was conducted, 47 subjects had received at least one dose of FT218 in this study. These consisted of 8 subjects in Group A and 39 subjects in Group B. None of these subjects had completed the study. 3 subjects in Group A discontinued from the study (1 subject based on a decision by the investigator and the other 2 subjects for other reasons). 8 subjects in Group B discontinued from the study (1 subject based on a decision by the investigator, 5 subjects based on their own decision, and 1 subject for other reasons).

The overall disposition of subjects is also summarized in the following extract from an applicant table.

Subject Disposition
All Subjects

	Group A, FT218	Group B, FT218	Overall
Screened	9	40	49
Safety Population [1]	8 (88.9%)	39 (97.5%)	47 (95.9%)
Number of Subjects Completing the Study	0	0	0
Number of Subjects Prematurely Discontinuing the Study	3 (33.3%)	5 (12.5%)	8 (16.3%)

The subjects enrolled were all ≥ 17 years old, with a mean age of 34.4 years. 63.8% of subjects were female and 78.7% were white.

9.2.2 Subject Exposure

Days of exposure to study medication are summarized in the following applicant table.

Summary of Days of Study Drug Exposure
Safety Population

FT218 Dose Level Statistic	Group A, FT218 (N=8)	Group B, FT218 (N=39)	Overall (N=47)
Total of all Dose Levels (days)			
n	8	39	47
Mean (SD)	96.6 (73.22)	102.3 (64.25)	101.3 (65.04)
Median	108.0	101.0	101.0
Min, Max	5, 171	3, 234	3, 234
4.5 g (days)			
n	8	2	10
Mean (SD)	27.4 (55.22)	10.0 (14.14)	23.9 (49.48)
Median	8.0	10.0	8.0
Min, Max	5, 164	0, 20	0, 164
6.0 g (days)			
n	6	8	14
Mean (SD)	44.0 (52.47)	22.9 (37.25)	31.9 (43.86)
Median	25.5	7.0	7.0
Min, Max	7, 145	3, 110	3, 145

FT218 Dose Level Statistic	Group A, FT218 (N=8)	Group B, FT218 (N=39)	Overall (N=47)
7.5 g (days)			
n	2	26	28
Mean (SD)	145.0 (15.56)	76.2 (72.24)	81.1 (71.89)
Median	145.0	61.0	81.0
Min, Max	134, 156	1, 207	1, 207
9.0 g (days)			
n	0	22	22
Mean (SD)		82.1 (64.66)	82.1 (64.66)
Median		94.0	94.0
Min, Max		1, 234	1, 234

Note: N is the number of subjects in the safety population. Subjects are summarized by study group.

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The overall duration of dosing in each treatment group is summarized in the next applicant table.

Group	Number of Subjects Dosed with FT218		
	1-3 Months	4-6 Months	>6 Months
Group A	4	4	0
Group B	13	20	6
Total	17	24	6

9.2.3 Adverse Events

9.2.3.1 Overall Summary Of Treatment-Emergent Adverse Events

A total of 15 patients (3 [37.5%] in Group A and 12 [30.8%] in Group B) had treatment-emergent adverse events. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation. These data are summarized in the following applicant table.

Category	Group A, FT218 (N=8)	Group B, FT218 (N=39)	Overall (N=47)
Subjects with at least one TEAE	3 (37.5%)	12 (30.8%)	15 (31.9%)
Subjects with at least one TEAE related to treatment [1]	1 (12.5%)	6 (15.4%)	7 (14.9%)
Subjects with an AE leading to treatment discontinuation	0	0	0
Subjects with at least one TEAE leading to temporary discontinuation or dose adjustment	1 (12.5%)	0	1 (2.1%)
Subjects with an AE leading to death	0	0	0
Subjects with at least one SAE	0	0	0

Abbreviations: TEAE = Treatment emergent adverse event; SAE = Serious treatment emergent adverse event.
Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the safety population. Subjects are summarized by study group. Number of subjects experiencing an event and percentage of subjects experiencing an event are summarized. AEs were coded using MedDRA version 23.0. TEAEs are events that occurred or worsened on or after the first dose of study drug.
[1] AEs with a relationship of related, possibly, or missing were considered related.

9.2.3.2 Individual Adverse Events

Individual adverse events that occurred in at least one subject in either treatment group are summarized in the following table by preferred term.

Preferred Term	Group A (Total N = 8 subjects) N (%)	Group B (Total N = 39 subjects) N (%)
Splenic lesion	0	1 (2.6)
Vertigo positional	0	1 (2.6)
Abdominal pain upper	0	1 (2.6)
Nausea	1 (12.5)	2 (5.1)
Rectal hemorrhage	0	2 (5.1)
Toothache	0	1 (2.6)
Vomiting	1 (12.5)	2 (5.1)
Fatigue	0	1 (2.6)
Pyrexia	0	1 (2.6)
COVID-19	0	1 (2.6)
Pharyngitis streptococcal	0	1 (2.6)
Concussion	0	1 (2.6)
Contusion	0	2 (5.1)
Fall	0	2 (5.1)
Ligament sprain	0	1 (2.6)
Road traffic accident	0	1 (2.6)
Skin abrasion	0	1 (2.6)
Weight decreased	0	1 (2.6)
Insulin resistance	0	1 (2.6)
Arthralgia	0	1 (2.6)
Neck pain	0	1 (2.6)
Dizziness	0	1 (2.6)
Headache	0	1 (2.6)
Tremor	0	1 (2.6)
Nightmare	0	1 (2.6)
Dysuria	0	1 (2.6)
Oropharyngeal cobble stone mucosa	0	1 (2.6)
Oropharyngeal pain	0	2 (5.1)
Erythema	0	1 (2.6)
Urticaria	0	1 (2.6)

9.2.3.3 Safety Laboratory Tests

There are no items of special concern in regard to FT218 in the applicant's display and analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during this study.

9.2.3.4 Vital Signs

The changes observed in systolic and diastolic blood pressure, and in heart rate during this study were unremarkable.

9.3 Applicant's Conclusions

The applicant's key conclusions were the following:

- The data for Study CLFT218-1901 indicated that FT218 was generally well-tolerated with the safety data for that study being consistent with the safety experience in Study CLFT218-1501.

- No new safety data were observed in Study CLFT218-1901 that changed the overall assessment of the safety of CLFT218-1901.

9.4 Reviewer's Summary Comments

9.4.1 Study Design

The main features of the design of this study were as follows:

- The primary objective of this study was to investigate the long-term safety and tolerability of FT218. Secondary objectives of this study included evaluating the safety and tolerability (and dosing regimens) when switching from twice-nightly sodium oxybate immediate-release to FT218.

- This was to be an open-label uncontrolled study of 24 months duration.

- Subjects to be enrolled in this study were to consist of patients with either Type 1 or Type 2 narcolepsy and were to be in 2 groups: Group A, consisting of about 100 subjects who completed Study CLFT218-1501; and Group B, consisting of about 150 subjects who were currently receiving twice-nightly sodium oxybate.

- The study was to have 3 consecutive dosing periods: Period 1, a dose-titration period lasting 1-2 months; Period 2, a stable-dose period lasting up to 24 months; and Period 3, a follow-up period lasting 1 week.

- The dosing regimen for each group during Study Period 1 is summarized as follows: for Group A, dosing with FT218 once nightly was to begin at a dose of 4.5 g nightly, with weekly increments of 1.5 g nightly until the highest tolerated dose up to a maximum of 9.0 g nightly was reached or the dose deemed effective by the investigator was reached (titration up or down was permitted); for Group B, dosing with FT218 once nightly was to begin at a dose equivalent or closest to the total gram dose of twice-

nightly sodium oxybate; that dose was then to be titrated up or down as determined by the investigator.

- Safety outcome measures were to include adverse events, vital signs, safety laboratory tests, and electrocardiograms.

9.4.2 Study Results

The results of this ongoing study are as summarized in the 120-Day Safety Update to this NDA, submitted on April 13, 2021, and are based on an interim analysis of safety, dated February 26, 2021.

At the time the above safety analysis was conducted, 47 patients had received at least one dose of FT218 in this study; they consisted of 8 patients in Group A and 39 patients in Group B; and none of these subjects had completed the study. 3 patients in Group A and 8 patients in Group B had by then withdrawn from the study, with none of these patients discontinuing the study on account of adverse events. No patient in Group A and only 6 patients in Group B had been exposed to study medication for > 6 months.

There were no deaths, serious adverse events, or discontinuations due to adverse events seen in the study. The pattern of adverse events in that study was generally consistent with what had been observed in Study CLFT218-1501 and with other oxybate products. Vital sign and laboratory data revealed no items of significant concern.

The patient exposure to FT218 in this study was limited in regard to both the number of subjects exposed as well as duration of exposure.

10. Additional Clinical Studies Of Sodium Oxybate Extended-Release For Oral Suspension (FT218)

The additional clinical studies of FT218 that have been conducted have been clinical pharmacology studies.

In this section, a summary of those studies has been provided, together with a summary of adverse event data from each.

10.1 Overall Summary

A table summarizing the clinical pharmacology and biopharmaceutics studies of FT218 is below. The table is extracted from a larger table already in Section 7 of this review.

Note that Study PKFT218-1801 was considered a pivotal bridging study directed at demonstrating that the FT218 was comparable in total exposure with Xyrem®.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report Location of Study Report
PK	PKFT218-1603	To assess the effect of food on sodium oxybate for extended release oral suspension (FT218) formulation administered at 6 g in healthy volunteers	An open-label, randomized, single dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover study Control: None	Treatment A: 6 g FT218 after a 10-hour fast Treatment B: 6 g FT218 30 minutes after the start of a standardized high-fat breakfast Powder for oral suspension, Oral	Enrolled: 16 Completed: 15	Healthy subjects	Single Dose	Completed; Full 5.3.1.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1301	To assess Sodium Oxybate in human plasma samples and to determine the corresponding pharmacokinetic parameters of three controlled release formulations of a single dosing of sodium oxybate CR taken 2 hours post-evening standardized meal, versus two divided doses of marketed reference Xyrem® taken 4 hours apart, first intake 2 hours post-evening standardized meal then 4 hours later	Single-dose, open-label, randomized Control: EU-approved Xyrem®	**Periods 1-4**: Randomized to: Test Product A: Single dose sodium oxybate CR type 1, 4.5 g Test Product B: Single dose sodium oxybate CR type 2, 4.5 g Test Product C: Single dose sodium oxybate CR type 3, 4.5 g Reference Product: Two divided doses Xyrem®, 2.25 g each **Period 5**: Randomized to receive: Test Product B: Single dose sodium oxybate CR type 2, 6 g Test Product C: Single dose sodium oxybate CR type 3, 6 g Powder for oral suspension, Oral (FT218)	Enrolled: 16 Completed: **Periods 1 -4**: Test Product A: 12 subjects Test Product B: 12 subjects Test Product C: 12 subjects Reference Product: 12 subjects **Period 5**: Test Product B: 7 subjects Test Product C: 6 subjects	Healthy subjects	FT218: Single dose Xyrem®: Two doses	Completed; Legacy 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA	PKFT218-1602	To assess the relative bioavailability and safety of sodium oxybate for extended release oral suspension (FT218) formulation (single dose of 6 g) versus the marketed reference Xyrem® (at the dose of 2 x 3 g) in healthy volunteers	A comparative, open label, randomized, 2 period, 2 sequence crossover relative bioavailability study Control: EU-approved Xyrem®	Two periods: FT218: Single dose of 6 g Xyrem®: 3 g, twice, 4 hours apart Powder for oral suspension, Oral (FT218)	Enrolled: 28 Completed: 26	Healthy subjects	FT218: Single dose Xyrem®: Two doses	Completed; Full 5.3.1.2
BE	PKFT218-1701	To demonstrate the bioequivalence of two FT218 batches (single dose of 4.5 g) in healthy volunteers	A comparative, open-label, randomized, 2-stage sequential design, 2 period, crossover study Control: None	Treatment A: 4.5 g of FT218 batch MP2 Treatment B: 4.5 g of FT218 batch MP4 Powder for oral suspension, Oral	Enrolled: 22 Completed: 21	Healthy subjects	Single Dose	Completed; Full 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
BA	PKFT218-1801	To demonstrate assess the relative bioavailability of FT218 when compared with the reference listed product, U.S. Xyrem® in healthy volunteers	A Comparative, Open-Label, 2-Period, Randomized, Sequential Design, Crossover Study Control: U.S.-approved Xyrem®	Treatment A: Single-dose of 6 g FT218 (powder for oral suspension) Treatment B: Single-dose of 6 g U.S. Xyrem® (oral solution) Powder for oral suspension, Oral	Enrolled: 28 Complete: 28	Healthy subjects	Single dose	Completed; Full 5.3.1.2
PK	PKFT218-1802	To assess the pharmacokinetics of two FT218 batches (single dose administered of 6 g) in healthy volunteers	An exploratory, open-label, randomized, 2 treatments, 2 periods, 2 sequences crossover study Control: None	Treatment A: Single dose of 6 g FT218 MP4 Batch A Treatment B: Single dose of 6 g FT218 MP4 Batch B Powder for oral suspension, Oral	Dosed in Period 1: 20 Completed: 18	Healthy subjects	Single dose	Completed; Full 5.3.1.2

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1902	To assess the pharmacokinetics of four 6 g single-doses of once-nightly sodium oxybate (FT218) formulations with varying release rates in healthy volunteers	An open label, randomized, 4-treatment, 4-period, 4-sequence crossover study Control: None	Formulation A: (b) (4) Formulation B: (b) (4) Formulation C: (b) (4) Formulation D: (b) (4) Powder for oral suspension, Oral	Enrolled: 36 Completed: 35	Healthy subjects	Single dose	Completed; Full 5.3.3.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1702	To assess the drug-drug interaction of divalproex sodium extended release (ER) at steady-state on FT218 formulation administered at a single 6 g dose in healthy volunteers	An open-label, sequential study Control: None	Treatment 1: 6 g FT218 Treatment 2: Daily administration of 1250 mg/day divalproex sodium ER to reach steady-state Treatment 3: Co-administration of 1250 mg divalproex sodium ER and 6 g FT218, with divalproex sodium ER administered first Powder for oral suspension, Oral	Enrolled: 24 Completed: 22 Evaluable for PK analysis:21	Healthy subjects	Treatment 1: Day 1 Treatment 2: Days 2-11 Treatment 3: Day 12	Completed; Full 5.3.3.1

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
PK	PKFT218-1901	To assess the drug-drug interaction of divalproex sodium extended release (ER) at steady-state on FT218 formulation administered at a single 6 g evening dose in healthy male volunteers	An open-label, sequential study Control: None	Treatment 1: 6 g FT218 Treatment 2: Daily administration of 1250 mg/day divalproex sodium ER to reach steady-state Treatment 3: Co-administration of 1250 mg divalproex sodium ER and 6 g FT218, with divalproex sodium ER administered first Powder for oral suspension, Oral	Enrolled: 24 Completed: 23	Healthy subjects	Treatment 1: Day 1 Treatment 2: Days 2-11 Treatment 3: Day 12	Completed; Full 5.3.3.1
BA	PKFT218-1601	To assess the pharmacokinetics and safety for sodium oxybate for extended release oral suspension (FT218) formulation after single dose administrations at doses of 4.5, 7.5, and 9 g in healthy volunteers.	An open-label, 3-period study Control: None	Three different doses of FT218 in a sequential order: Treatment A: Single dose 4.5 g FT218 Treatment B: Single dose 6 g FT218 Treatment C: Single dose 9 g FT218 Powder for oral suspension, Oral	Enrolled: 20 Completed: 12	Healthy subjects	Single dose	Completed; Full 5.3.3.4

10.2 Adverse Event Data For Individual Studies

Adverse event data for the individual studies summarized in the table above are below.

Data for safety laboratory tests, vital signs, and electrocardiograms did not yield any findings of clinical significance.

10.2.1 PKFT218-1301

The following applicant table summarizes adverse event data for Study PKFT218-1301. The data are self-explanatory and the number of adverse events small under each category. No serious adverse events were noted during this study.

Body System	Adverse Event	FT218, 4.5 g Number of Events n=38	FT218, 6 g Number of Events n=24	FT218, 7.5 g Number of Events n=22	Xyrem® Number of Events n=13
Gastrointestinal Disorders	Gastroenteritis	1	0	0	0
	Nausea	1	1	1	1
	Abdominal pain upper	0	4	0	0
Infections and Infestations	Pharyngitis	1	1	0	0
	Influenza	1	0	0	0
	Rhinitis	0	1	0	0
Musculoskeletal disorders	Arthralgia	1	0	0	0
Nervous System Disorders	Headache	0	0	0	1
	Dizziness	0	0	1	0

10.2.2 PKFT218-1601

The following applicant table summarizes adverse event data for Study PKFT218-1601. The data are self-explanatory and the number of adverse events small under each category. However, one adverse event was graded as serious: a patient developed pronounced sedation associated with vomiting 2 hours after receiving a 9 g dose of FT218 (without prior titration).

Body System	Adverse Event	FT218 4.5 g Number of Events (% of Subjects) n=20 Subjects	FT218 7.5 g Number of Events (% of Subjects) n=20 Subjects	FT218 9 g Number of Events (% of Subjects) n=12 Subjects
Gastrointestinal Disorders	Abdominal discomfort	0 (0)	1 (5)	0 (0)
	Abdominal pain	1 (5)	0 (0)	0 (0)
	Diarrhea	0 (0)	1 (5)	2 (16.7)
	Feces soft	0 (0)	0 (0)	1 (8.3)
	Nausea	0 (0)	1 (5)	2 (16.7)
	Vomiting	0 (0)	1 (5)	3 (25)
General Disorders and Administration Site Conditions	Feeling drunk	0 (0)	1 (5)	1 (8.3)
Infections and Infestations	Gastroenteritis viral	1 (5)	0 (0)	0 (0)
	Nasopharyngitis	1 (5)	0 (0)	0 (0)
Nervous Disorders	Headache	5 (20)	1 (5)	2 (16.7)
	Sedation	0 (0)	0 (0)	2 (16.7)
Psychiatric Disorders	Nightmare	0 (0)	0 (0)	1 (8.3)
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	0 (0)	0 (0)	1 (8.3)
Social Circumstances	Stress at work	0 (0)	1 (5)	0 (0)
Vascular Disorders	Thrombophlebitis superficial	0 (0)	0 (0)	1 (8.3)

10.2.3 PKFT218-1701

The following applicant table summarizes adverse event data for Study PKFT218-1701. The data are self-explanatory and the number of adverse events small under each category. No serious adverse events were observed.

Body System	Adverse Event	FT218 4.5 g, Batch MP2 Number of Events (% of Subjects) (n=22)	FT218 4.5 g, Batch MP4 Number of Events (% of Subjects) (n=21)
Cardiac Disorders	Palpitations	1 (5)	0 (0)
Gastrointestinal Disorders	Nausea	1 (5)	2(5)
	Dry Mouth	1 (5)	0 (0)
General Disorders and Administration Site Conditions	Feeling drunk	1 (5)	0 (0)
	Feeling Hot	0 (0)	1 (5)
	Catheter Site Hematoma	1 (5)	0 (0)
	Vessel Puncture Site Hematoma	1 (5)	0 (0)
Musculoskeletal Disorders	Myalgia	1 (5)	0 (0)
Nervous Disorders	Headache	3 (14)	2 (10)
	Somnolence	3 (14)	6 (29)
	Dizziness	0 (0)	2 (10)
	Restless Leg Syndrome	0 (0)	1 (5)
Psychiatric Disorders	Anxiety	2 (5)	0 (0)
	Insomnia	1 (5)	0 (0)
Reproductive System and Breast Disorders	Dysmenorrhea	0 (0)	1 (5)

10.2.4 PKFT218-1602

The following applicant table summarizes adverse event data for Study PKFT218-1602. The data are self-explanatory and the number of adverse events small under most categories. The most frequent adverse event in those treated with FT218 was somnolence, an adverse event to be expected with oxybate compounds. No serious adverse events were observed.

Body System	Adverse Event	FT218 6 g Number of Events (% of Subjects) (n=27)	Xyrem® 6 g Number of Events (% of Subjects) (n=27)
Ear	Vertigo	1 (3.7)	2 (7.4)
Eye	Asthenopia	0 (0)	1 (3.7)
Gastrointestinal	Nausea	3 (11.1)	2 (7.4)
	Abdominal discomfort	0 (0)	2 (7.4)
	Abdominal pain	2 (7.4)	0 (0)
	Vomiting	3 (3.7)	0 (0)
General Disorders and Administration Site Conditions	Feeling drunk	3 (11.1)	2 (7.4)
	Feeling hot	2 (7.4)	2 (7.4)
	Catheter Site pain	2 (7.4)	2 (3.7)
	Fatigue	1 (3.7)	2 (7.4)
	Influenza like illness	0 (0)	2 (7.4)
	Asthenia	0 (0)	1 (3.7)
	Catheter site hematoma	0 (0)	1 (3.7)
	Catheter site inflammation	0 (0)	1 (3.7)
	Feeling of relaxation	0 (0)	1 (3.7)
	Malaise	1 (3.7)	0 (0)
Infections and Infestations	Rhinitis	0 (0)	3 (11.1)
	Nasopharyngitis	0 (0)	1 (3.7)
	Pneumonia	0 (0)	1 (3.7)
Injury, Poisoning and Procedural Complications	Lip injury	1 (3.7)	0 (0)
Nervous Disorders	Somnolence	9 (33.3)	6 (22.2)
	Dizziness	1 (3.7)	4 (14.8)
	Headache	1 (3.7)	4 (11.1)
	Paresthesia	1 (3.7)	2 (7.4)
	Dizziness postural	2 (7.4)	0 (0)
	Ataxia	1 (3.7)	0 (0)
	Syncope	1 (3.7)	0 (0)

Body System	Adverse Event	FT218 6 g Number of Events (% of Subjects) (n=27)	Xyrem® 6 g Number of Events (% of Subjects) (n=27)
Psychiatric Disorders	Euphoric mood	2 (7.4)	1 (3.7)
	Insomnia	2 (7.4)	0 (0)
	Restlessness	1 (3.7)	0 (0)
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	1 (3.7)	3 (11.1)
	Skin irritation	1 (3.7)	0 (0)
Vascular Disorders	Hot flush	1 (3.7)	1 (3.7)

10.2.5 PKFT218-1603

The following applicant table summarizes adverse event data for Study PKFT218-1603. The data are self-explanatory and the number of adverse events small under most categories. The most frequent adverse events in those treated with FT218 were nausea, vomiting, and somnolence, adverse events which are to be expected with oxybate compounds. No serious adverse events were observed.

Body System	Adverse Event	FT218, Fasted Conditions Number of Events (% of Subjects) (n=16)	FT218, Fed Conditions Number of Events (% of Subjects) (n=15)
Eye	Vision Blurred	1 (6.3)	0 (0)
Gastrointestinal	Nausea	7 (37.5)	2 (6.7)
	Vomiting	3 (18.8)	1 (6.7)
	Abdominal pain	0 (0)	2 (13.3)
General Disorders and Administration Site Conditions	Feeling Drunk	4 (25.0)	4 (26.7)
	Fatigue	3 (18.8)	1 (6.7)
	Asthenia	0 (0)	1 (6.7)
Infections and Infestations	Nasopharyngitis	2 (12.5)	0 (0)
Nervous Disorders	Somnolence	17 (81.3)	12 (66.7)
	Dizziness	7 (43.8)	3 (20.0)
	Headache	4 (25.0)	2 (13.3)
	Hypotonia	3 (18.8)	2 (13.3)
	Hypoesthesia	2 (12.5)	0 (0)
	Visual Pathway Disorder	1 (6.3)	0 (0)
Psychiatric Disorders	Anxiety	1 (6.3)	0 (0)
	Confusional State	0 (0)	1 (6.7)
	Euphoric Mood	1 (6.3)	0 (0)
	Mood Altered	0 (0)	1 (6.7)
Respiratory Disorders	Dry Throat	1 (6.3)	0 (0)

10.2.6 PKFT218-1702

The following applicant table summarizes adverse event data for Study PKFT218-1702. The data are self-explanatory and the number of adverse events small under most categories. The most frequent adverse events in those treated with FT218 were somnolence, dizziness, and nausea, adverse events which are to be expected with oxybate compounds. No serious adverse events were observed, but one patient who received FT218 vomited after receiving that drug on Day 1 and discontinued study participation.

Body System	Adverse Event	FT218 Number of Events (% of Subjects) (n=24)	DVP[1] Number of Events (% of Subjects) (n=23)	FT218 + DVP Number of Events (% of Subjects) (n=22)
Ear Disorders	Vertigo	0 (0)	0 (0)	3 (13.6)
	Ear congestion	0 (0)	1 (4.3)	0 (0)
	Tinnitus	0 (0)	1 (4.3)	0 (0)
Eye Disorders	Photophobia	1 (4.2)	0 (0)	0 (0)
Gastrointestinal Disorders	Nausea	5 (20.8)	6 (26.1)	1 (4.5)
	Diarrhea	1 (4.2)	2 (8.7)	0 (0)
	Vomiting	2 (8.3)	0 (0)	0 (0)
	Abdominal discomfort	0 (0)	1 (4.3)	0 (0)
	Abdominal distention	1 (4.2)	0 (0)	0 (0)
	Abdominal pain	1 (4.2)	0 (0)	0 (0)
General Disorders and Administration Site Conditions	Fatigue	3 (12.5)	1 (4.3)	
	Catheter Site Related Reaction	0 (0)	1 (4.3)	1 (4.5)
	Feeling drunk	1 (4.2)	1 (4.3)	0 (0)
	Catheter site inflammation	1 (4.2)	0 (0)	0 (0)
	Catheter site pain	0 (0)	0 (0)	1 (4.5)
	Feeling abnormal	1 (4.2)	0 (0)	0 (0)
	Feeling hot	1 (4.2)	0 (0)	0 (0)
	Vessel puncture site bruise	0 (0)	1 (4.3)	0 (0)
	Vessel puncture site pain	0 (0)	1 (4.3)	0 (0)
Metabolism and Nutrition Disorders	Decrease appetite	0 (0)	0 (0)	2 (9.1)
Musculoskeletal and Connective Tissue Disorders	Limb discomfort	1 (4.2)	0 (0)	0 (0)
	Myalgia	0 (0)	1 (4.3)	0 (0)

Body System	Adverse Event	FT218 Number of Events (% of Subjects) (n=24)	DVP[1] Number of Events (% of Subjects) (n=23)	FT218 + DVP Number of Events (% of Subjects) (n=22)
Nervous Disorders	Somnolence	14 (54.2)	2 (8.7)	11 (40.9)
	Dizziness	10 (41.7)	3 (8.7)	6 (27.3)
	Headache	1 (4.2)	6 (21.7)	1 (4.5)
	Ataxia	0 (0)	0 (0)	2 (9.1)
	Disturbance in attention	0 (0)	1 (4.3)	0 (0)
	Presyncope	0 (0)	1 (4.3)	0 (0)
	Tremor	0 (0)	0 (0)	1 (4.5)
Psychiatric Disorders	Insomnia	1 (4.2)	0 (0)	0 (0)
	Libido increased	1 (4.2)	0 (0)	0 (0)
Respiratory Disorders	Cough	0 (0)	1 (4.3)	0 (0)
	Dyspnea	0 (0)	0 (0)	1 (4.5)
	Epistaxis	0 (0)	1 (4.3)	0 (0)
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	2 (8.3)	1 (4.3)	0 (0)
	Blister	0 (0)	1 (4.3)	0 (0)
	Dry skin	0 (0)	1 (4.3)	0 (0)
	Rash generalized	0 (0)	0 (0)	1 (4.5)

[1] Divalproex sodium 1250 mg

10.2.7 PKFT218-1801

The following applicant table summarizes adverse event data for Study PKFT218-1801. The data are self-explanatory and the number of adverse events small under most categories. The most frequent adverse events in those treated with FT218 were somnolence, dizziness, nausea, and vomiting, adverse events which are to be expected with oxybate compounds. No serious adverse events were observed.

Body System	Adverse Event	FT218 6 g Number of Events (% of Subjects) (n=28)	Xyrem® 6 g Number of Events (% of Subjects) (n=28)
Ear and labyrinth disorders	Vertigo	1 (4)	1 (4)
Eye disorders	Asthenopia	1 (4)	0 (0)
Gastrointestinal disorders	Constipation	0 (0)	1 (4)
	Dry mouth	0 (0)	1 (4)
	Nausea	8 (29)	3 (11)
	Vomiting	3 (11)	3 (11)
General disorders and administration site conditions	Chills	0 (0)	1 (4)
	Feeling cold	1 (4)	0 (0)
	Feeling hot	1 (4)	1 (4)
Nervous system disorders	Dizziness	7 (25)	7 (25)
	Dysarthria	1 (4)	1 (4)
	Headache	2 (7)	2 (7)
	Lethargy	1 (4)	1 (4)
	Somnolence	3 (11)	4 (14)
Respiratory, thoracic and mediastinal disorders	Apnea	1 (4)	1 (4)
	Hypopnea	1 (4)	0 (0)
Skin and subcutaneous tissue disorders	Hyperhidrosis	0 (0)	1 (4)
	Rash	1 (4)	0 (0)
Vascular disorders	Peripheral coldness	0 (0)	1 (4)

10.2.8 PKFT218-1802

The following applicant table summarizes adverse event data for Study PKFT218-1802. The data are self-explanatory and the number of adverse events small under most categories. The most frequent adverse events in those treated with FT218 were somnolence, dizziness, nausea, and vomiting, adverse events which are to be expected with oxybate compounds. No serious adverse events were observed.

Body System	Adverse Event	FT218, M4 Batch A Number of Events (% of Subjects) (n=20)	FT218, M4 Batch B Number of Events (% of Subjects) (n=18)
Gastrointestinal	Nausea	3 (15.0)	4 (22.2)
	Abdominal pain	1 (5.0)	1 (5.6)
	Vomiting	1 (5.0)	0 (0)
General Disorders and Administration Site Conditions	Fatigue	3 (15.0)	3 (16.7)
	Catheter Site Bruise	1 (5.0)	1 (5.6)
	Catheter Site Pain	1 (5.0)	1 (5.6)
	Feeling Drunk	1 (5.0)	0 (0)
	Malaise	1 (5.0)	0 (0)
Infections and Infestations	Chlamydial Infection	1 (5.0)	0 (0)
Musculoskeletal and Connective Tissue Disorders	Myalgia	2 (10.0)	0 (0)
	Musculoskeletal stiffness	0 (0)	1 (5.6)
Nervous Disorders	Somnolence	3 (15.0)	1 (5.6)
	Dizziness	2 (10.0)	2 (11.1)
	Dizziness postural	1 (5.0)	0 (0)
Psychiatric Disorders	Sleep disorder	3 (15.0)	0 (0)
	Panic attack	1 (5.0)	0 (0)
Respiratory Disorders	Dyspnea	1 (5.0)	1 (5.6)
Skin and subcutaneous tissue disorders	Hyperhidrosis	1 (5.0)	0 (0)
Vascular Disorders	Hematoma	0 (0)	1 (5.6)

10.2.9 PKFT218-1901

The following applicant table summarizes adverse event data for Study PKFT218-1901. The data are self-explanatory and the number of individual adverse events small. No serious adverse events were observed.

Body System	Adverse Event	FT218 Number of Events (% of Subjects) (n=24)	DVP[1] Number of Events (% of Subjects) (n=24)	FT218 + DVP[1] Number of Events (% of Subjects) (n=23)
Ear Disorders	Vertigo	3 (12.5)	0	1 (4.3)
	Ear discomfort	0 (0)	2 (8.3)	0 (0)
	Tinnitus	0 (0)	1 (4.2)	0 (0)
Eye Disorders	Vision blurred	0 (0)	0 (0)	2 (8.7)
Gastrointestinal Disorders	Nausea	2 (8.3)	4 (16.7)	3 (13.0)
	Dry mouth	1 (4.2)	1 (4.2)	0 (0)
	Abdominal discomfort	1 (4.2)	0 (0)	0 (0)
	Abdominal pain	0 (0)	1 (4.2)	0 (0)
	Diarrhea	0 (0)	1 (4.2)	0 (0)
	Flatulence	1 (4.2)	0 (0)	0 (0)
	Paresthesia oral	0 (0)	0 (0)	1 (4.3)
General Disorders and Administration Site Conditions	Fatigue	1 (4.2)	5 (16.7)	4 (17.4)
	Feeling of relaxation	2 (8.3)	0 (0)	1 (4.3)
	Catheter site pain	0 (0)	1 (4.2)	0 (0)
	Chest pain	0 (0)	1 (4.2)	0 (0)
	Feeling drunk	0 (0)	0 (0)	1 (4.3)
	Feeling hot	0 (0)	2 (4.2)	0 (0)
	Vessel puncture site pain	1 (4.2)	0 (0)	0 (0)
Infections and Infestations	Nasopharyngitis	0 (0)	1 (4.2)	0 (0)
Injury, poisoning and procedural complications	Skin abrasion	0 (0)	1 (4.2)	0 (0)
Metabolism and Nutrition Disorders	Decrease appetite	0 (0)	2 (8.3)	1 (4.3)

Body System	Adverse Event	FT218 Number of Events (% of Subjects) (n=24)	DVP[1] Number of Events (% of Subjects) (n=24)	FT218 + DVP[1] Number of Events (% of Subjects) (n=23)
Musculoskeletal and Connective Tissue Disorders	Groin pain	0 (0)	1 (4.2)	0 (0)
	Muscle twitching	1 (4.2)	0 (0)	0 (0)
	Muscular weakness	1 (4.2)	0 (0)	0 (0)
	Myalgia	1 (4.2)	0 (0)	0 (0)
Nervous Disorders	Dizziness	6 (20.8)	2 (4.2)	3 (13.0)
	Somnolence	2 (8.3)	1 (4.2)	3 (13.0)
	Headache	0 (0)	2 (8.3)	1 (4.3)
	Ataxia	0 (0)	0 (0)	1 (4.3)
	Dizziness postural	1 (4.2)	0 (0)	0 (0)
	Paresthesia	1 (4.2)	0 (0)	0 (0)
	Poor quality sleep	1 (4.2)	0 (0)	0 (0)
Psychiatric Disorders	Abnormal dreams	1 (4.2)	1 (4.2)	2 (8.7)
	Insomnia	0 (0)	1 (4.2)	0 (0)
Respiratory Disorders	Dry throat	0 (0)	2 (8.3)	0 (0)
	Oropharyngeal pain	0 (0)	1 (4.2)	0 (0)
Skin and Subcutaneous Tissue Disorders	Dry skin	0 (0)	3 (12.5)	0 (0)

[1] Divalproex sodium 1250 mg

10.2.10 PKFT218-1902

The following applicant table summarizes adverse event data for Study PKFT218-1902. The data are self-explanatory and the number of individual adverse events small in most instances. The most common adverse event was nausea.

Body System	Adverse Event	Treatment A Number of Events (% of Subjects) (n=36)	Treatment B Number of Events (% of Subjects) (n=35)	Treatment C Number of Events (% of Subjects) (n=36)	Treatment D Number of Events (% of Subjects) (n=36)
Ear Disorders	Vertigo	0 (0)	0 (0)	0 (0)	1 (2.8)
Gastrointestinal Disorders	Nausea	5 (13.9)	5 (14.3)	4 (11.1)	5 (13.9)
	Vomiting	1 (2.8)	1 (2.9)	0 (0)	1 (2.8)
	Abdominal pain	0 (0)	0 (0)	1 (2.8)	0 (0)
	Toothache	0 (0)	0 (0)	0 (0)	1 (2.8)
General Disorders and Administration Site Conditions	Catheter site bruise	1 (2.8)	3 (8.6)	1 (2.8)	3 (8.3)
	Feeling hot	1 (2.8)	2 (5.7)	1 (2.8)	0 (0)
	Medical Device Site Reaction	1 (2.8)	1 (2.9)	1 (2.8)	0 (0)
	Catheter Site Hematoma	0 (0)	0 (0)	2 (5.6)	0 (0)
General Disorders and Administration Site Conditions (continued)	Vessel puncture site bruise	0 (0)	1 (2.9)	1 (2.8)	0 (0)
	Catheter site pain	0 (0)	0 (0)	0 (0)	1 (2.8)
	Fatigue	1 (2.8)	0 (0)	0 (0)	0 (0)
	Thirst	0 (0)	0 (0)	0 (0)	1 (2.8)
Infections and Infestations	Herpes zoster	0 (0)	0 (0)	0 (0)	1 (2.8)
	Nasopharyngitis	0 (0)	1 (2.9)	0 (0)	0 (0)
Musculoskeletal and Connective Tissue Disorders	Myalgia	1 (2.8)	1 (2.9)	1 (2.8)	1 (2.8)
	Pain in extremity	2 (5.6)	0 (0)	0 (0)	0 (0)
	Back pain	1 (2.8)	0 (0)	0 (0)	0 (0)
Nervous Disorders	Headache	7 (19.4)	7 (20.0)	2 (5.6)	8 (19.4)
	Dizziness	5 (13.9)	5 (11.4)	3 (8.3)	3 (8.3)
	Somnolence	2 (5.6)	1 (2.9)	4 (11.1)	4 (11.1)
	Ataxia	0 (0)	3 (8.6)	0 (0)	1 (2.8)
	Dizziness postural	0 (0)	0 (0)	1 (2.8)	1 (2.8)
	Tremor	1 (2.8)	1 (2.9)	0 (0)	1 (2.8)
	Paresthesia	1 (2.8)	0 (0)	0 (0)	0 (0)
	Restless Leg syndrome	0 (0)	0 (0)	0 (0)	1 (2.8)
Psychiatric Disorders	Insomnia	1 (2.8)	0 (0)	0 (0)	0 (0)
	Nervousness	1 (2.8)	0 (0)	0 (0)	0 (0)

Body System	Adverse Event	Treatment A Number of Events (% of Subjects) (n=36)	Treatment B Number of Events (% of Subjects) (n=35)	Treatment C Number of Events (% of Subjects) (n=36)	Treatment D Number of Events (% of Subjects) (n=36)
Reproductive System and Breast Disorders	Dysmenorrhea	0 (0)	1 (2.9)	0 (0)	0 (0)
Respiratory Disorders	Cough	0 (0)	0 (0)	0 (0)	1 (2.8)
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	0 (0)	1 (2.9)	1 (2.8)	0 (0)
Vascular Disorders	Hot flush	0 (0)	0 (0)	0 (0)	2 (5.6)

10.3 Pharmacokinetic Data

The review of the pharmacokinetic data from the studies summarized in this section has been deferred to the clinical pharmacology staff.

10.4 Reviewer's Summary Comments

The safety data in these studies were generally consistent with those observed in other clinical trials of oxybate products, including other clinical trials of FT218.

11. Additional Safety Data Supporting Current Application

In addition to the safety data for FT218 submitted with this application, the applicant has reviewed the following:

- Publicly available safety data for Xyrem, including the most recent label for that product.
- Safety data for Xyrem/sodium oxybate published since April 2018 (the date being agreed to with the Agency at the Pre-NDA meeting held on July 7, 2020).
- The FDA Adverse Event Reporting System.

The above data have been summarized and appear not to provide any significant new safety information for sodium oxybate.

In addition, the following are drawn attention to.

- No instances of drug overdose were observed with FT218.

- A detailed analysis indicated that FT218 is expected to have no greater abuse potential than currently marketed oral solution formulations of oxybate (note that the Agency's Controlled Substances Staff have also reviewed this application).

- There were no instances of withdrawal or rebound during the clinical development of FT218.

- *In vitro* data indicate that the controlled-release properties of FT218 can be overcome by co-ingestion or suspension in alcohol, a finding that is to be addressed in the proposed Prescribing Information by contraindicating the concomitant use of FT218 and alcohol.

12. Review Of Proposed Prescribing Information And Related Documents

I have reviewed the Prescribing Information proposed by the applicant together with the applicant proposals for a number of linked documents, namely the Medication Guide, Instructions for Use, and, to a limited extent, the Risk Evaluation and Mitigation Strategy (REMS).

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

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

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

As this aspect of my review has been complex and iterative, it is not possible to summarize here the basis for every recommendation that I have made regarding the Prescribing Information and related documents.

I am however in agreement with the versions of the Prescribing Information, Medication Guide, and Instructions for Use as finalized at the time this review was completed.

Dr. Tracy Peters who is the Associate Director of Labeling in this Division, has played a primary role in drafting both the Prescribing Information and related documents.

13. Summary Of Statistical Review

The primary statistical review of this NDA has been performed by Dr. Xiaorong (Sharon) Yan of the Division of Biometrics I. Her review was completed on September 24, 2021.

Her review has been directed at the efficacy results Study CLFT218-1501, as derived from the analysis of the primary efficacy endpoints for that study.

She has concluded that Study CLFT218-1501 has provided sufficient evidence that FT218 is effective as compared with placebo in treating cataplexy and excessive daytime sleepiness in patients with narcolepsy. She has substantiated the applicant's main efficacy analyses.

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

14. Summary Of Nonclinical Review

The primary nonclinical review of this NDA was completed by Dr. Chun-Ting David Lee on June 17, 2022.

Dr. Lee has concluded that Lumryz is approvable from a nonclinical perspective; however, previous studies of (b) (4) in multiple species suggest the potential for systemic toxicity that warrants further assessment as a post-marketing required study. The sponsor will be required to conduct an oral absorption study of radiolabeled (b) (4) in rat. If oral absorption of (b) (4) is demonstrated in rat, then a 6-month oral toxicology study of (b) (4) in rat will be needed. Further recommendations regarding these studies are in his review.

I agree with the conclusions and recommendations in this review.

15. Summary Of Clinical Pharmacology Review

This review was completed by Dawei Li, PhD, and Bilal Abu Asal, PhD, of the Division of Neuropsychiatric Pharmacology of the Office of Clinical Pharmacology. Their full review was finalized on October 14, 2021, with an addendum to that review being finalized on May 24, 2022.

The review, supplemented by its addendum, contains a detailed description of the pharmacokinetic studies conducted during the development of FT218. Please refer to that review for full details.

The descriptions of the following studies in that review are of particular note: PKFT218-1801 and PKFT218-1901. Those descriptions are there summarized below.

15.1 Study PKFT218-1801

Study PKFT218-1801 was a key relative bioavailability study intended to bridge the finding of safety and efficacy of Xyrem, the listed drug, to FT218. In that study conducted in 23 healthy adults, the pharmacokinetics of a single oral 6.0 g dose of FT218 (taken 2 hours after an evening meal) was compared with that of two oral doses of 3.0 g doses of Xyrem (the first dose being taken 2 hours after the evening meal, and the second dose a further 4 hours later).

In that study, the geometric means for the $AUC_{0\text{-}t}$, $AUC_{0\text{-}infinity}$, and C_{max} [all based on concentrations of gamma-hydroxybutyrate (GHB)] for FT218 were comparable with those for Xyrem with their 90% confidence intervals within the 80% to 125% range, and were thus sufficient to show comparable total exposure; those results were considered sufficient to bridge to the prior finding of safety and effectiveness of Xyrem. The following table, copied from this review, displays the above data;

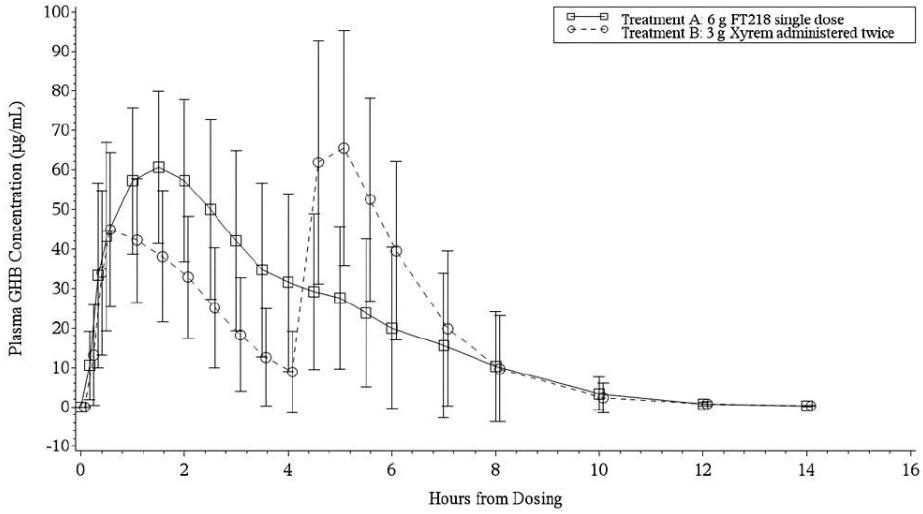
Table 4. Summary of Relative Bioavailability Study (PKFT218-1801)

PK parameter (unit)	Geometric LS means				Geometric mean ratio	90% CI	Intra-subject %CV
	n	Test (A)	n	Reference (B)			
$AUC_{0\text{-}t}$ (µg•h/mL)	23	241.09	23	234.37	102.87	97.96, 108.02	9.58
$AUC_{0\text{-}inf}$ (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;

However, the concentration-time profiles of GHB for FT218 were different from those for Xyrem as displayed in the following figure copied from this review; as a result, the Phase 3 efficacy study of FT218, CLFT218-1501 was necessary.

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;

At FT218 doses of 7.5 g and 9.0 g, GHB exposure was expected to be lower than those after the administration of Xyrem at the same doses, as the dose-proportionality profile for FT218 is different from that for Xyrem.

15.2 Study PKFT218-1901

This study investigated the potential drug-drug interaction between FT218 and divalproex sodium. In the submission, the sponsor noted the following, that suggested the potential for such an interaction: the absorption of GHB is facilitated by sodium/proton-dependent monocarboxylate transporter activity which is inhibited by valproic acid in the intestine and at the blood-brain barrier; and valproic acid also inhibits GHB dehydrogenase, the enzyme that converts GHB to succinic acid semialdehyde.

In this study, 24 healthy adult men received the following in succession: FT218 6 g on Day 1; divalproex sodium extended-release 1250 mg/day from Day 2 to Day 11; and the co-administration of divalproex sodium extended-release 1250 mg and FT218 6 g on Day 12 (with divalproex sodium extended-release administered first).

The C_{max}, AUC_{0-t}, and $AUC_{0-infinity}$ for GHB following the co-administration of divalproex sodium extended-release 1250 mg and FT218 6 g was compared with those following the administration of FT218 6 g alone. The results of that analysis are displayed in the following table, copied from the review.

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

Treatment Comparison (Test vs. Reference)	PK Parameter	Geometric LS means				Ratio Test/Reference 90% CI			
		Test	n	Reference	n	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
	$AUC_{0\text{-}inf}$ (h·µg/mL)	347	22	295	22	117.52	111.99	123.32	9.3
	$AUC_{0\text{-}t}$ (h·µg/mL)	340	23	289	23	117.42	112.09	123.01	9.2

Source: PKFT218-1901 CSR Table S3 on 12;

The clinical pharmacology reviewers noted that the 90% confidence for the ratios for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}infinity}$ were within the standard limits of bioequivalence (80% to 125% range).

Based on the above results, the reviewers concluded that the impact of the co-administration of divalproex sodium with FT218 on the pharmacokinetics of FT218 was not clinically significant, and therefore did not recommend a specific dose adjustment when the two drugs were co-administered. Although Avadel's drug-drug interaction study did not include pharmacodynamic endpoints, the review team considered the design of this study to be adequate to assess pharmacokinetics and safety information associated with coadministration of Lumryz and divalproex sodium extended-release. However, the reviewers did note that since divalproex sodium is a sedative anti-epileptic drug that may lead to central nervous system depression, the potential of a pharmacodynamic interaction between Lumryz (also a central nervous system depressant) and divalproex sodium cannot be ruled out.

The reviewers recommended text for the Prescribing Information for FT218 that included a description of the above study in section 12.3 of the Prescribing Information. The reviewers also stated that statements in section 5.1 of the Prescribing Information regarding the general risks associated with concomitant administration of FT218 with other central nervous system depressants (including, but not limited to, sedating antiepileptic drugs) are sufficient to inform prescribers of the general risks of administering FT218 and divalproex sodium concomitantly. This reviewer concurs fully with that view.

The reviewers for this discipline also note that the applicant conducted another study of the potential drug-drug interaction between FT218 and divalproex sodium; this was Study PKFT218-1702. The results of Study PKFT218-1702 were consistent with those of Study PKFT218-1901. However, in Study PKFT218-1702, FT218 and divalproex sodium were administered in the morning (2 hours after breakfast) whereas in Study PKFT218-1901, FT218 and divalproex

sodium were administered in the evening (2 hours after dinner), which was more consistent with the dosing recommendations for FT218. While standard safety assessments were performed during Study PKFT218-1702, no pharmacodynamic assessments were conducted during that study, either.

16. Summary Of Quality Assessment Review

This review was completed by a team that covered the following areas: Drug Substance, Drug Product, Manufacturing, Microbiology, and Biopharmaceutics. The review was completed on September 9, 2021.

The overall application team lead for that review was Martha Heimann, PhD.

This review team recommended that the Agency approve this NDA for Lumryz™, stating that, "*from a quality perspective this application, as amended during the review, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients*."

For further details, please see the full text of that review.

17. Summary Of Office Of Surveillance And Epidemiology Reviews

17.1 Review By Division Of Risk Management (DRM)

In this NDA, the applicant has proposed a Risk Evaluation and Mitigation Strategy (REMS) for FT218.

The proposed REMS has been reviewed primarily by the staff of the Division of Risk Management of the Office of Surveillance and Epidemiology, although staff of this Division have also been closely involved with the review of that REMS.

The REMS itself is comprised of multiple documents.

This reviewer has been involved to only a limited extent with the review of the REMS for FT218.

The review of this REMS was completed on July 14, 2022, by the following staff: Bob Pratt, PharmD; Anahita Tavakoli, MA; and Joseph Paradis, PharmD. Their review found the proposed Lumryz REMS, and its appended materials as submitted on July 14, 2022, to be acceptable and recommended approval of the Lumryz REMS. The conclusions and recommendations in this review were acceptable to this reviewer.

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

A review of the report of a human factors validation study and components of labeling was conducted by Ankara Yokum, PharmD, of the Division of Medical Error Prevention and Analysis (DMEPA). Her review was completed on October 5, 2021.

Her review concluded that the results of the human factors validation study were acceptable. She recommended changes to the container and carton labeling which were accepted by this reviewer. Please see the full text of that review for further details.

18. Summary Of Office Of Prescription Drug Promotion (OPDP) Review

An Office of Prescription Drug Promotion labeling review was completed by Lynn Panholzer, PharmD, on October 19, 2021: this review focused on the proposed Prescribing Information, and the container and carton labels for Lumryz. OPDP's comments advised the review team on particular statements within the proposed labeling that could be viewed as promotional in nature. Those comments were considered by the review team, and where appropriate, incorporated when the labeling was finalized.

19. Summary Of Patient Labeling Review

A patient labeling review was completed on October 14, 2021, by Marcia Williams, PhD, of the Division of Medical Policy Prog, and Samuel Fasanmi, PharmD, of the Office of Prescription Drug Promotion. This review focused on the proposed Medication Guide and Instructions for Use. Changes to both documents were recommended in this review. Those recommendations were considered by the review team and, where appropriate, incorporated when the labeling was finalized.

20. Summary of Controlled Substances Staff Review

A review of this application by James Tolliver, PhD, of the Controlled Substances Staff, was completed on August 25, 2021.

Among the key conclusions and recommendations in his review are the following.

- As a product containing sodium oxybate, FT218 will, once approved, be in Schedule III of the Controlled Substances Act.

- The incidence of adverse events possibly indicative of an abuse potential was low in clinical trials of FT218.

- Lumryz should be distributed under a Risk Evaluation and Mitigation Strategy (REMS).

21. Financial Disclosure Information

Financial disclosure information has submitted for the following studies: CLFT218-1501, CLFT218-1301, CLFT218-1601, CLFT218-1602, CLFT218-1603, CLFT218-1701, CLFT218-1801, CLFT218-1901, and CLFT218-1903.

21.1 Components Of Certification

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

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

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

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

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

21.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of any of the clinical studies that were submitted with this application.

22. Site Inspection Report

At an internal meeting held on February 9, 2021, it was concluded that an inspection of study sites participating in the clinical efficacy and safety study CLFT218-1501 was not necessary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review of the analytical part of Study PKFT218-1801; an onsite inspection was

not possible on account of the Covid-19 pandemic. After the submission of additional documents by the company conducting the bioanalyses, the reviewer, Makini Cobourne-Duval, PhD, concluded that deficiencies noted in the initial study inspection did not have an impact on the reliability of the study results.

23. Division Of Pediatric And Maternal Health Memorandum

A memorandum was completed by Denise J Pica-Branco of the Division of Pediatric and Maternal Health (DPMH) on October 6, 2021. This memorandum followed a request from this Division, which, in turn, followed a request from the 505(b)(2) Committee, and was connected primarily with the text of the proposed Prescribing Information for FT218.

Among the comments made in this memorandum were the following:

- This applicant was granted Orphan Drug Designation for Sodium Oxybate Extended-Release for Oral Suspension (FT218) for the treatment of narcolepsy on January 8, 2018. Thus, the Pediatric Research Equity Act (PREA) is not applicable to this product.

- This applicant is not seeking the approval of Sodium Oxybate Extended-Release for Oral Suspension (FT218) for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in children.

- (b) (4)

24. Priority Review Request

24.1 Priority Review Request

The original submission of this application was accompanied by a Priority Review Request.

In this Priority Review Request, the applicant had asserted that a once-nightly regimen of FT218 if approved, would provide a significant improvement in the safety and effectiveness of the treatment of cataplexy and excessive daytime sleepiness in narcolepsy compared to currently available therapies including the currently approved twice nightly formulations of Xywav and Xyrem. The main reasons for this assertion are the following:

- A once-nightly regimen allows patients and their spouses/partners to avoid the anxiety and disruption related to waking for a second nightly dose.

- A once-nightly regimen improves compliance and thus the efficacy of Lumryz and the quality of life of patients.

- The need to awaken to take the second dose of an oxybate formulation increases the risk of adverse events.

24.2 Agency Response

In a filing communication dated February 26, 2021, the Agency granted this application a Standard Review, rather than a Priority Review.

25. 505(b)(2) Regulatory-Related Issues

An applicant seeking approval of an NDA submitted pursuant to section 505(b)(2) of the FD&C Act that relies on one or more listed drugs must submit with its NDA an appropriate patent certification or statement with respect to certain patents for such relied-upon listed drugs (see section 505(b)(2)(A) and (B) of the FD&C Act and 21 CFR 314.50(i)(1)(i)-(iii)). The manner in which this applicant addressed patents listed in the Orange Book for Xyrem, the listed drug relied upon, have been the subject of extensive discussion among the staff of the Office of New Drug Policy, Office of Regulatory Policy, and other Agency staff.

Of particular note, the applicant provided section 505(b)(2)(B) statements to address the following patents listed in the Orange Book for Xyrem: 7,668,730 (’730) patent, 8,731,963 (’963) patent, 8,772,306 (’306) patent, 9,050,302 (’302) patent, 9,486,426 (’426) patent, 10,213,400 (’400) patent, 10,864,181 (’181) patent, and 11,253,494 (’494) patent. The Agency’s analysis related to the applicant’s patent statements is reflected in a memo-to-file dated May 24, 2022, by Maarika Kimbrell, JD, Director of the Office of New Drug Policy, Office of New Drugs.

In a letter issued on May 24, 2022, Maarika Kimbrell, JD, Director of the Office of New Drug Policy, informed the applicant of the Agency’s conclusion that that the applicant’s proposed section 505(b)(2)(B) statement to address the ’963 patent was inappropriate. The reasons for the Agency’s conclusion are explained in detail in that letter and the May 24, 2022, memo. The letter also stated that the applicant must provide an appropriate patent certification under 314.50(i)(1)(i) to address the ’963 patent.

On June 6, 2022, Avadel submitted a “Paragraph IV” patent certification for the ’963 patent. The June 6, 2022, application no longer included a 505(b)(2)(B) statement to the ‘730 patent. On June 7, 2022, Avadel submitted documentation “of timely sending and receipt of notice of Paragraph IV certification to the owner

of the patent and holder of the associated new drug application." In a submission dated June 22, 2022, Avadel notified the Agency of patent infringement litigation filed by Jazz Pharmaceuticals, Inc. (Jazz) with respect to the '963 patent that "was brought before expiration of 45 days from the date of receipt of Avadel's Paragraph IV notice pursuant to Section 505(c)(3)(C) of the Act." The referenced patent litigation was filed on May 12, 2021. On June 30, 2022, the Agency provided clarification to Avadel that the May 12, 2021, patent infringement litigation did not occur within the 45-day period initiated by the receipt of notice of Paragraph IV patent certification. Therefore, Jazz's May 12, 2021, complaint for patent infringement with respect to the '963 patent did not give rise to a 30-month stay of approval of Avadel's NDA. The 45-day period described in section 505(c)(3)(C) of the FD&C Act has not yet expired, and this application is only eligible for a tentative approval at this time. If a patent infringement action is brought prior to the expiration of 45 days from the later of the date the notice provided under section 505(b)(3) is received by the patent owner or approved application holder, this application would be subject to a 30-month stay of approval, unless other conditions are met.

26. Overall Conclusions

Substantial evidence of the efficacy of FT218 for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in adults is provided by the single efficacy study CLFT218-1501 and through reliance on FDA's finding of safety and effectiveness for Xyrem, which is approved for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy based on adequate and well-controlled efficacy studies. FT218 demonstrated comparable total exposure to Xyrem for the $AUC_{0\text{-}t}$, $AUC_{0\text{-}infinity}$, and C_{max} [all based on concentrations of gamma-hydroxybutyrate (GHB)]. Because the concentration-time profiles of GHB for FT218 were different from those for Xyrem, a Phase 3 efficacy study of FT218, CLFT218-1501 was required; these results support the efficacy of the once nightly dosing regimen.

The adverse event profile of Lumryz is not substantially different from that of the approved proprietary oxybate products, Xyrem. The other components of the safety profile of Lumryz do not reveal any data of significant clinical concern. Thus, the main safety concerns related to the clinical use of Lumryz™, as with other oxybate products, are the following: central nervous system depression; and abuse and misuse.

The safety profile of FT218 is acceptable in support of its approval, assuming that its clinical use will be as recommended in the Prescribing Information and as set forth under the final Risk Evaluation and Mitigation Strategy (REMS) for that product.

FT218 has been demonstrated to have comparable total exposure to Xyrem in Study PKFT218-1801.

27. Recommendation

I recommend that Lumryz be approved for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy in adults. However, the 45-day period described in section 505(c)(3)(C) of the FD&C Act has not yet expired, and this application is only eligible for a tentative approval at this time.

Ranjit B. Mani, MD
Medical Reviewer

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/s/

RANJIT B MANI
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