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APPLICATION NUMBER:

212690Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	212690 (0001)
Sponsor:	Jazz Pharmaceuticals, Inc.
Drug:	JZP-258*
Proposed Indication:	Narcolepsy
Material Submitted:	New Drug Application
Correspondence Date:	1/21/20
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Date Review Completed	7/21/20
Reviewer:	Ranjit B. Mani, M.D.

*The original full name for this product is JZP-258 (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate), oral solution, 0.5 g/mL. Further, the brand name XYWAV (Xywav) has been assigned this product.

TABLE OF CONTENTS

Executive Summary	2
1. Background	7
2. Contents Of Submission	8
3. Contents Of Review	9
4. Proposed Indication For JZP-258	10
5. History Of Clinical Development Of JZP-258	10
6. Chemistry And Related Items	11
7. Overview Of Clinical Studies Of JZP-258	11
8. Outline Of Main Clinical Efficacy Study (Study 15-006)	12
9. 120-Day Safety Update	52
10. Additional Clinical Studies Of JZP-258	52
11. Additional Safety Data Supporting Current Application	64
12. Review Of Proposed Prescribing Information And Related Documents	64
13. Risk Evaluation And Mitigation Strategy (REMS)	65
14. Summary Of Statistical Review	66
15. Summary Of Nonclinical Review	66
16. Summary Of Clinical Pharmacology Review	67
17. Summary Of Quality Assessment (Chemistry) Review	67
18. Summary Of Office Of Surveillance And Epidemiology Reviews	68
19. Patient Labeling Review	68

20.	Summary Of Office Of Prescription Drug Promotion (OPDP) Reviews	69
21.	Controlled Substances Staff Review	69
22.	Pediatric Labeling Review	70
23.	Financial Disclosure Information	70
24.	Site Inspection Report	71
25.	Pediatric Waiver	71
26.	Overall Conclusion.....	72
27.	Recommendation.....	72

Executive Summary

Recommendation

I recommend that JZP-258 be approved for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

Proposed Indications

This New Drug Application (NDA) seeks the approval of JZP-258 for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

Background To Application

JZP-258 is an aqueous oral solution of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate, 0.5 g/mL (total salt concentration), equivalent to 0.413 g/mL of oxybate, the active moiety. JZP-258 has been developed as a lower-sodium alternative to Xyrem® (sodium oxybate oral solution [500 mg/mL]), which is notable for its high sodium content.

Xyrem® is currently approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years or older with narcolepsy. Xyrem® is available only through a Risk Evaluation and Mitigation Strategy (REMS).

The proposed proprietary name for JZP-258 is XYWAV (Xywav).

Clinical Studies Of JZP-258

- A main clinical efficacy and safety study (Study 15-006).

- Two clinical pharmacology studies (Studies 13-010 and JZP258-010)
- A study investigating the taste of JZP-258 (Study 15-00#)

All clinical studies of JZP-258 have been conducted in adults.

Summary of Main Clinical Study Supporting This Application

Study 15-006 is the main clinical study supporting this NDA. Key aspects of this study are summarized below.

Study Design

Protocol 15-006 had the following main features:

- The primary objective of the study was to evaluate the efficacy of JZP-258 in the treatment of cataplexy in patients with narcolepsy. A key secondary objective was to evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness in patients with narcolepsy.
- This was a double-blind, placebo-controlled, randomized withdrawal multicenter study of the efficacy and safety of JZP-258. Patients enrolled in the study included those whose prior treatment status was in any of the following categories:
 1. Treatment with a stable dose of Xyrem® alone for at least 2 months prior to screening.
 2. Treatment with a stable dose of Xyrem® and an unapproved anti-cataplectic for at least 2 months prior to screening.
 3. Treatment with an unapproved anti-cataplectic, but no treatment with Xyrem®.
 4. No prior treatment with Xyrem® or an unapproved anti-cataplectic.
- The study consisted of the following consecutive periods: screening; open-label titration and treatment optimization (of variable duration up to a maximum of 12 weeks, depending on prior treatment status); open-label stable dose treatment (2 weeks); double-blind randomized withdrawal (2 weeks); and safety follow-up (2 weeks). All study patients (i.e., patients in all 4 entry categories) were to be titrated (during the variable-duration open-label titration period) to a dose of JZP-258 that was deemed both effective and tolerable and was maintained for at least 2 weeks prior to entering the two-week open-label stable-dose period.
- A total of about 185 patients were planned to be enrolled in the study, of whom about 130 patients were expected to enter the double-blind

withdrawal period during which they were to be randomly assigned 1:1 to either continuing the same dose of JZP-258 taken during the stable dose period or to placebo.

- The main inclusion criteria for this study were as follows: men and women, aged 18 to 70 years; a primary diagnosis of narcolepsy with cataplexy that met the ICSD-3 criteria or DSM-5 criteria; a history of having at least 14 cataplexy attacks in a typical two-week period and clinically significant symptoms of excessive daytime sleepiness prior to any narcolepsy treatment; treatment status prior to study entry consisting of one of the aforementioned 4 categories; if currently treated with Xyrem, must have had documented improvement documented clinical improvement of cataplexy and excessive daytime sleepiness; and if treated with a stimulant for narcolepsy must have been at an unchanged dose for at least 2 months prior to dosing or must not have been treated at all with a stimulant.
- The primary efficacy parameter was the change in weekly number of cataplexy attacks from the 2-week stable-dose period to the 2-week double-blind treatment period. The key secondary efficacy parameter was the change in Epworth Sleepiness Scale score from the end of the 2-week stable-dose period to the end of the 2-week double-blind randomized-withdrawal treatment period. A number of other efficacy endpoints were also under evaluation in this study, including the Patient Global Impression of Change for narcolepsy overall; the Clinical Global Impression of Change for narcolepsy overall; the change in quality of life based on the Short Form-36 score; and EuroQol 5 Dimensions Self-Report Questionnaire.
- Safety measures were to include adverse events, vital signs, weight, physical examinations, 12-lead electrocardiograms, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and the Columbia-Suicide Severity Rating Scale (for assessing suicidality).
- The final analysis of the primary efficacy parameter and key secondary efficacy parameters was to employ a fixed sequential testing strategy in which the initial step was to involve a comparison of JZP-258 with placebo for the primary efficacy parameter; if the initial comparison was statistically significant (currently $p \leq 0.05$), the treatment groups would then be compared on the key secondary efficacy parameter at the same level of statistical significance (currently $p \leq 0.05$). An analysis of covariance model was to be used at both steps.
- The main study was to be followed by an open-label extension study (phase) lasting 24 weeks.

Study Results

Study 15-006 was conducted in a manner consistent with the study protocol.

201 patients were enrolled in the study. They consisted of: 52 patients who were receiving Xyrem only; 23 patients were receiving a combination of Xyrem and another (unapproved) anti-cataplectic drug; 36 patients were on a non-Xyrem (unapproved) anti-cataplectic drug; and 90 patients were drug-naïve at study entry. All 201 patients entered the main study in the optimized treatment and titration period (12 weeks). 155 patients completed that period, of whom 149 patients entered the stable-dose period (2 weeks). 144 out of 149 patients completed the stable-dose period.

136 out of 144 patients who completed the stable-dose period were then randomized, entering the randomized, double-blind, placebo-controlled, withdrawal period (2 weeks). At the beginning of that period, 69 patients were randomized to JZP-258 and 67 patients were randomized to placebo; all 69 patients randomized to JZP-258 and all 59 patients randomized to placebo completed the study.

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two-week randomized withdrawal period in the weekly number of cataplexy attacks was 11.46 for the placebo group and 0.12 for the group that continued to take JZP-258 (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring JZP-258 over placebo were seen on the key secondary efficacy parameter analyzed in the prespecified sequence: the change from baseline in modified Epworth Sleepiness Scale score was 3.0 in the placebo group and 0.0 in the group that continued to take JZP-258 ($p < 0.0001$).

74 patients then entered the open-label extension study; 67 patients completed that part of the study.

The adverse event profile of JZP-258 as seen in this study was not substantially different from that seen with Xyrem. The other safety outcomes did not reveal any data of concern.

Additional Clinical Studies Of JZP-258

The additional clinical studies conducted with JZP-258 included:

- Two clinical pharmacology studies.
 - Study 13-010, a randomized, open-label cross-over study in healthy subjects, primarily intended to compare the relative bioavailability

and bioequivalence of JZP-258 with Xyrem under fasting and fed conditions.

- Study JZP258-101, a randomized open-label crossover study intended to compare the relative bioavailability and bioequivalence of JZP-258 with Xyrem under fasting conditions.
- A randomized, double-blind, placebo-controlled crossover study in healthy subjects evaluating the taste of JZP-258 (Study 15-003)

The safety profile of JZP-258, as seen in this study, was not substantially different from that seen with sodium oxybate alone (i.e., with Xyrem®).

Pharmacokinetic and other data from the first two of the above studies are summarized later in this review; importantly, neither Study 13-010 nor Study JZP258-101 provided evidence that JZP-258 is bioequivalent to Xyrem.

Proposed Labeling And Risk Evaluation And Mitigation Strategy (REMS)

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

Conclusion

Substantial evidence of the efficacy of JZP-258 for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy is provided by single efficacy Study 15-006, with confirmatory evidence coming from the prior finding of efficacy of Xyrem (sodium oxybate, i.e., containing the same active moiety) for the same indication as that proposed for JZP-258.

The safety profile of JZP-258 is acceptable, and not substantially different from that seen with Xyrem.

1. Background

This New Drug Application (NDA) seeks the approval of JZP-258 for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

This New Drug Application has been submitted under the Section 505(b)(1) pathway.

The full name for this product, as stated in the cover letter for this submission, is as follows: JZP-258 (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate), oral solution, 0.5 g/mL. The proposed trade name for this product is XYWAV™, which is also referred to as “Xywav” in this review.

JZP-258 is described in the cover letter to this submission as “an aqueous oral solution of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate, 0.5 g/mL, equivalent to 0.413 g/mL of oxybate, the active moiety.”

JZP-258 has been developed as a lower-sodium alternative to Xyrem (sodium oxybate oral solution [500 mg/mL]; see below), which is notable for its high sodium content. Sodium oxybate is another name for the sodium salt of gamma hydroxybutyrate.

The sodium content of the maximum total nightly dose of Xyrem® is 9 grams, which has a sodium content of 1638 mg. The WARNINGS AND PRECAUTIONS section of the current product label for Xyrem® states that the high salt content of that product should be considered in patients sensitive to a high salt intake (such as those with heart failure, hypertension, or renal impairment). On the other hand, the sodium content of the maximum dose of JZP-258 is 131 mg.

Xyrem (sodium oxybate oral solution [500 mg/mL]) is currently approved in this country for the treatment of cataplexy and excessive daytime in narcolepsy. Xyrem was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. 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 (and still is) 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. A formal Risk Evaluation and Mitigation Strategy (REMS) for Xyrem was approved 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. The sponsor has proposed that in accordance with 65 FR 13235 and 21 CFR 1308.13 Schedule III (c) (6), JZP-258 should also be placed into Schedule III upon Agency approval of that product.

This NDA for JZP-258 refers to NDA 21196 for Xyrem, for which Jazz Pharmaceuticals is also the sponsor and license holder; a Letter of Authorization from Jazz Pharmaceuticals, permitting the Agency to reference NDA 21196 for Xyrem accompanies the current application.

The submission of this application was preceded by the submission (under IND 49641, Serial Number 351), on October 21, 2019, of a notification of the sponsor's intention to redeem a priority review voucher (PRV) (Rare Pediatric Disease PRV BLA 125610). That voucher, which was granted at the time of approval of Biologics Licensing Application 12561, was purchased from Spark Therapeutics. This application was therefore granted Priority Review status.

Oxybate (gamma-hydroxybutyrate) is the active moiety in JZP-258 and in Xyrem®. Oxybate has been granted Orphan Drug Designation (#94-858) for the treatment of narcolepsy by the Agency on November 7, 1994.

In this review, the names "JZP-258" and "Xywav" have been used interchangeably.

Please note that this single review is intended to encompass all the following: primary clinical review; and team leader and cross-disciplinary team leader summary.

2. Contents Of Submission

This NDA submission has two main components.

- The original sNDA submission of January 21, 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: Regional.

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 16, 2020, which has also been provided in standard electronic Common Technical Document

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

Module 1: Regional.
Module 5. Clinical study reports.

Since the original submission of this sNDA, there have a number of additional communications such as, but not limited to, information requests and responses to those requests from the sponsor.

3. Contents Of Review

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

- History of clinical development of JZP-258.
- Chemistry and related items.
- Overview of clinical studies of JZP-258.
- Outline of main clinical efficacy study of JZP-258 (15-006).
- 120-Day Safety Update.
- Additional clinical studies of JZP-258.
- Additional safety data supporting current application.
- Review of proposed Prescribing Information and related documents.
- Risk Evaluation and Mitigation Strategy (REMS).
- 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.
- Patient labeling review.

- Summary of Office of Prescription Drug Promotion reviews.
- Controlled Substances Staff review.
- Pediatric labeling review.
- Financial disclosure information.
- Site inspection report.
- Pediatric waiver.
- Overall conclusion.
- Recommendation.

4. Proposed Indication For JZP-258

The proposed indication for JZP-258 is the treatment of cataplexy and excessive daytime sleepiness in patients 7 years and older with narcolepsy.

The above proposed indication is the same as that for which Xyrem is currently approved.

5. History Of Clinical Development Of JZP-258

JZP-258 has been developed under IND 49641, the same IND under which Xyrem was developed for the treatment of narcolepsy.

The development of JZP-258 for the treatment of narcolepsy was first discussed with the Agency at a Type C face-to-face meeting on December 2013.

Subsequently, there have been a number of further communications with the sponsor regarding this development program. These included, but were not limited to, the following:

- An End-of-Phase 2/Pre-Phase 3 meeting for which the preliminary response document issued by the Agency on September 18, 2015, together with additional clarifications provided to the sponsor, was considered to be sufficient.
- A Pre-NDA meeting held on October 2, 2019.

Please see the contents of the above communications regarding the development plan for JZP-258 for further details.

6. Chemistry And Related Items

JZP-258 is an aqueous solution of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate. This solution is intended for oral administration.

As per the sponsor, the content of each of above salts in the JZP-258 oral solution is as follows.

Salt	Content (per mL of JZP-258 oral solution)
Calcium oxybate	0.234 grams
Potassium oxybate	0.130 grams
Magnesium oxybate	0.096 grams
Sodium oxybate	0.040 grams

The pharmacologically-active moiety in both JZP-258 and Xyrem is oxybate (4-hydroxybutanoate or gamma-hydroxybutyrate [GHB]); GHB is, in turn, an endogenous compound and a metabolite of gamma-aminobutyric acid. JZP-258 is thus NOT designated as a New Molecular Entity.

According to the sponsor, the oral solution formulations of both JZP-258 and Xyrem contain the same concentration of active ingredient (0.5 g/mL) and the same concentration of active moiety, i.e., oxybate (0.413 g/mL).

The mechanism of action of oxybate in the treatment of narcolepsy is unknown. The current submission states the following: *"It is hypothesized that the therapeutic effects of Xyrem on cataplexy and EDS are mediated through GABAB actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons."* That statement is consistent with the text of the current Prescribing Information for Xyrem.

As with Xyrem, the total nightly dose of JZP-258 is to be administered in two equal divided doses 2.5 to 4 hours apart, with an effective and tolerable dose being reached by titration. The recommended starting dose, titration regimen, and maximum total nightly dosage in children are to be based on body weight.

7. Overview Of Clinical Studies Of JZP-258

The following clinical studies of JZP-258 have been conducted.

- Two clinical pharmacology studies.
 - Study 13-010, a randomized, open-label cross-over study in healthy subjects, primarily intended to compare the relative bioavailability and bioequivalence of JZP-258 with Xyrem under fasting and fed conditions.

- Study JZP258-101, a randomized open-label crossover study intended to compare the relative bioavailability and bioequivalence of JZP-258 with Xyrem under fasting conditions.
- A clinical efficacy and safety study.

Study 15-006, a double-blind, placebo-controlled, randomized-withdrawal study in patients with narcolepsy.

- A study evaluating the taste of JZP-258.

Study 15-003, a randomized, double-blind, placebo-controlled crossover study in healthy subjects.

Further details of these studies are in later sections of this review.

An efficacy and safety study of JZP-258 (i.e., Study 15-006) was required by the Agency, as bioequivalence could not be established between JZP-258 and Xyrem® for C_{max} of oxybate in either Study 13-010 or Study JZP258-101 under fasting conditions.

8. Outline Of Main Clinical Efficacy Study (Study 15-006)

This study was conducted in the following countries: Belgium, Croatia, Czech Republic, Finland, France, Germany, Holland, Poland, Spain, Switzerland, the United Kingdom, and the United States.

8.1 Outline Of Study Protocol

The sponsor conducted a single clinical efficacy study of JZP-258 after bioequivalence between JZP-258 and Xyrem could not be demonstrated on the C_{max} of oxybate.

The key elements of the final protocol for that efficacy study are summarized below. The version of Protocol 15-006 summarized below is that contained in Amendment #5, dated May 15, 2019.

8.1.1 Title

A Double-Blind, Placebo-Controlled, Randomized-Withdrawal Multicenter Study Of The Efficacy And Safety Of JZP-258 In Subjects With Narcolepsy With Cataplexy

8.1.2 Objectives

8.1.2.1 Primary Objective

To evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy.

8.1.2.2 Key Secondary Objective

To evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness in subjects with narcolepsy.

8.1.2.3 Secondary Objective

To evaluate the safety of JZP-258 in the treatment of subjects with narcolepsy.

8.1.2.4 Exploratory Objective

To characterize the conversion from other anti-cataplectic treatment regimens to JZP-258.

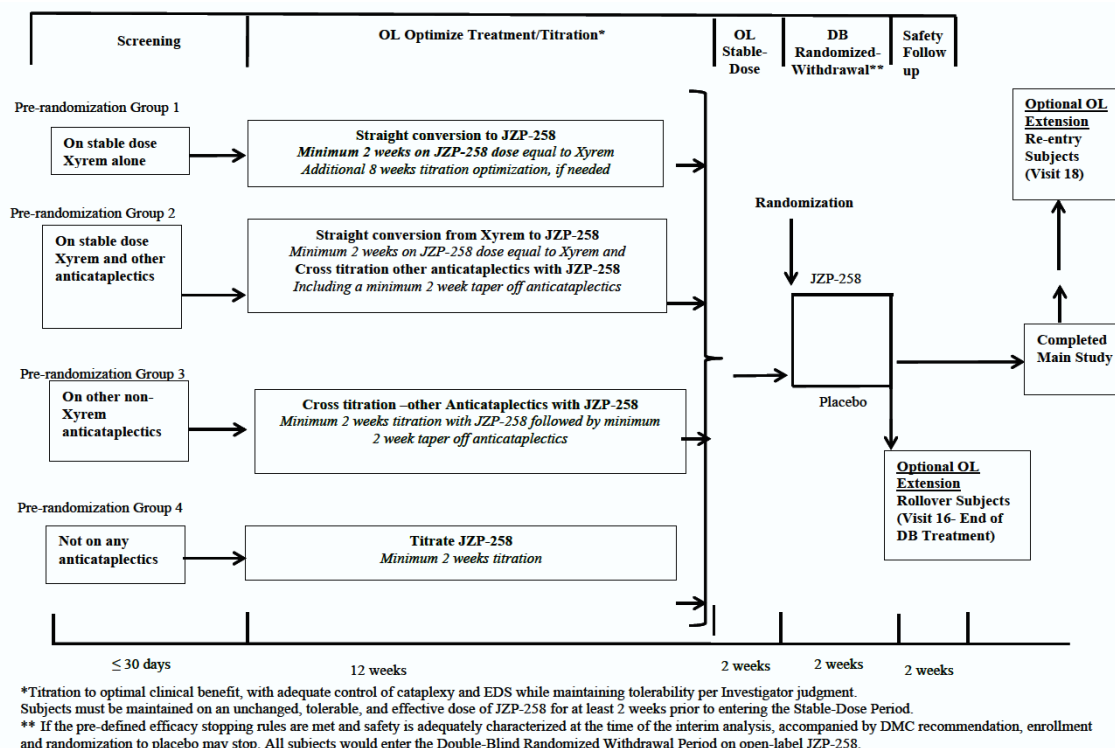
8.1.3 Design, Dose, Sample Size, And Duration

This (i.e., the main study) was to be a double-blind, placebo-controlled, randomized- withdrawal multicenter study of the efficacy and safety of JZP-258.

Those enrolled in the study were to include those whose prior treatment status is in any of the following categories:

- Treatment with stable dose of Xyrem alone (≤ 9 g/night) for at least 2 months prior to screening (Pre-Randomization Group 1).
- Treatment with a stable dose of Xyrem (≤ 9 g/night) and an unapproved anti-cataplectic for at least 2 months prior to screening (Pre-Randomization Group 2).
- Treatment with an unapproved anti-cataplectic, without Xyrem (Pre-Randomization Group 3).
- No prior treatment with Xyrem or an unapproved anti-cataplectic (Pre-Randomization Group 4).

All study patients (i.e., patients in all 4 entry categories above) were to eventually be titrated to a dose of JZP-258 that is deemed both effective and tolerable and is maintained for at least 2 weeks prior to entering the two-week open-label stable-dose period outlined in the schematic below.



Further details of the open-label titration period for each entry category are as follows.

- Patients (Pre-Randomization Group 1) receiving only a stable dose of Xyrem at study entry were to be switched to JZP-258 on a gram for gram (total nightly dose) basis, and were to remain on that dose of JZP-258 for a minimum of 2 weeks. If necessary, that dose of JZP-258 was to be further titrated over an additional 8 weeks. Subjects were to be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the stable dose period.
- Patients (Pre-Randomization Group 2) receiving a stable dose of Xyrem at study entry together with an unapproved anti-cataplectic medication were to first be switched to JZP-258 on a gram for gram (total nightly dose) basis, and were to remain on that dose of JZP-258 for a minimum of 2 weeks. They were then to be tapered off the unapproved anti-cataplectic medication over a minimum of 2 weeks, and for up to 8 weeks. If necessary, the dose of JZP-258 could be further titrated to a stable, tolerable, and effective dose over that 8-week period. Subjects were to be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the stable dose period.
- Patients (Pre-Randomization Group 3) receiving only an unapproved anti-cataplectic (and no Xyrem) at entry were to be first be titrated to a tolerable dose of JZP-258 over a minimum of 2 weeks at the start of that period. The dose of unapproved anti-cataplectic medication was then to be tapered off over a further 2 to 8 weeks. Next, if necessary, the dose of JZP-258 could be further titrated over a period of up to 8 weeks. Subjects were to be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the stable dose period.

- Patients (Pre-Randomization Group 4) not receiving any anti-cataplectic medication at entry were to receive JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during that period. Subjects were to be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the stable dose period.

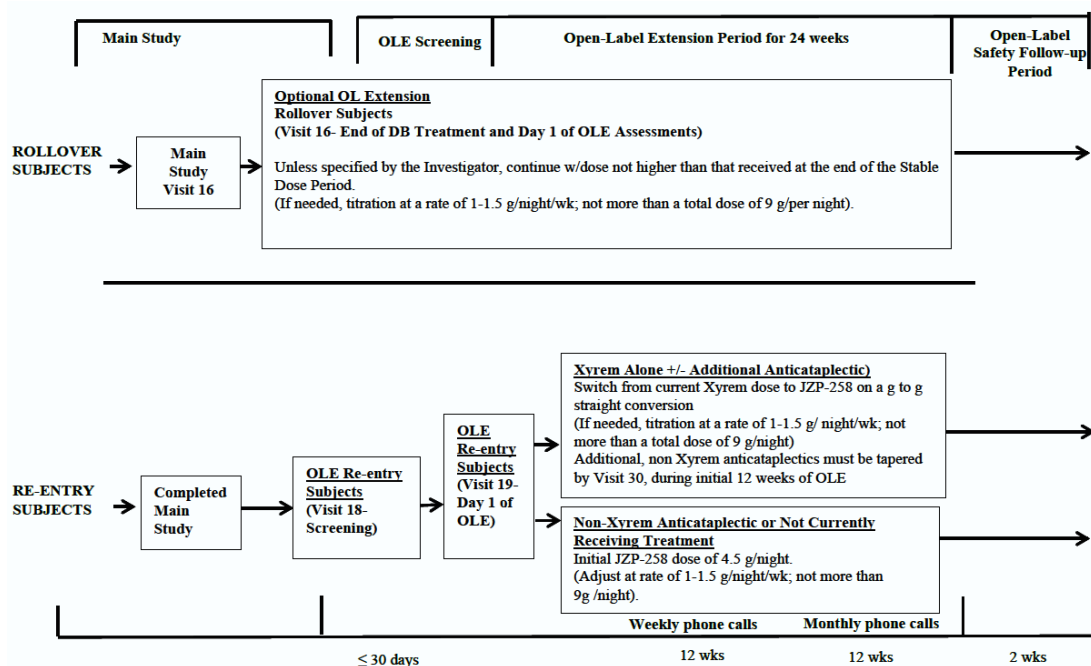
The open-label stable-dose period of 2 weeks was to be followed by a randomized withdrawal period also lasting 2 weeks: during that period, patients were to be randomized 1:1 to either continue to take the same dose of JZP-258 or to receive placebo.

A safety follow-up period of 2 weeks was to follow.

The main study was to be followed by an open-label extension study (phase) lasting 24 weeks. Patients could enter the open-label phase of the study in two categories, as further described immediately below.

- Rollover subjects: those who enter the open-label extension study directly from the main study, with Visit 16 being both the last day of the main study and first day of the open-label extension study.
- Re-entry subjects: those enter the open-label extension study sometime after completion of the main study.

The schematic for the open-label phase of the study is below.



About 185 subjects were to be enrolled in the study. It was hoped that as a result, 130 patients (65 patients per group) would enter the double-blind randomized withdrawal period.

8.1.4 Key Inclusion Criteria (For Main Study)

- Male or female. Age 18 to 70 years.
- Primary diagnosis of narcolepsy with cataplexy that meets the International Classification of Sleep Disorders (ICSD) – 3 criteria or DSM-5 criteria.
- History of having at least 14 cataplexy attacks in a typical two-week period and clinically significant symptoms of excessive daytime sleepiness prior to any narcolepsy treatment.
- Treatment status prior to study entry consisting of one the following:
 - Taking Xyrem® alone at unchanged doses (no greater than 9 g/night) for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening.
 - Taking Xyrem® at unchanged doses (no greater than 9 g/night) and an unapproved anti-cataplectic medication for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening.
 - Taking an unapproved anti-cataplectic and no Xyrem®.
 - Not receiving any medication for the treatment of cataplexy.
- If currently treated with Xyrem, must have documented clinical improvement of cataplexy and excessive daytime sleepiness as per the investigator's clinical judgment.
- Treated with a stimulant for narcolepsy at unchanged doses for at least 2 months prior to dosing or not treated at all with a stimulant.
- Using a medically-acceptable means of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception throughout the entire study period and for 30 days after the study is completed.
- Willing and able to comply with study procedures.
- Informed consent.

8.1.5 Key Exclusion Criteria (For Main Study)

These are below, taken from the latest version of the study protocol.

1. Narcolepsy secondary to another medical condition (e.g., central nervous system injury or lesion).
2. Restless leg syndrome (RLS) requiring treatment other than iron supplements.
3. Succinic semi-aldehyde dehydrogenase deficiency (SSADH).
4. Uncontrolled hypothyroidism.
5. History of seizures, excluding early childhood non-pathological febrile seizures.
6. History of head trauma associated with loss of consciousness in the past 5 years or if the event occurred more than 5 years prior to screening and the subject has sequelae due to the event.

7. Evidence of untreated or inadequately treated sleep-disordered breathing including:
 - a. Presence of clinically significant and untreated obstructive or central sleep apnea as determined by the Investigator or documented previously;or documentation of one of the following:
 - b. Apnea index >10 if on obstructive sleep apnea (OSA) treatment or untreated; or
 - c. Clinically significant hypoventilation; or
 - d. Noncompliance with primary OSA therapy. (Compliance defined as positive airway pressure use of ≥ 4 hours per night on $\geq 70\%$ of nights [≥ 5 of 7 nights/week], historical report [with Investigator concurrence] of use of an oral appliance on $\geq 70\%$ of nights [≥ 5 of 7 nights/week], or receipt of an effective surgical intervention for OSA symptoms.)
8. Parasomnias (e.g., sleep walking, rapid eye movement [REM] Sleep Behavior Disorder, etc.) felt by the investigator to negatively affect the conduct of the study. Parasomnia events associated with physical injury to the subject (or others) shall be discussed with the Medical Monitor.
9. Meets criteria for current major depression by clinical interview.
10. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness.
11. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
12. History or presence of any unstable or clinically significant medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or history or presence of another neurological disorder or surgical history that might affect the subject's safety and/or interfere with the conduct of the study in the opinion of the Investigator.
13. A current electrocardiogram (ECG) with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the Investigator at screening.
14. Any current clinically significant laboratory abnormality as determined by the Investigator at screening.
15. Is a female subject who is pregnant, nursing, or lactating.
16. A positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject).
17. Treatment with any central nervous system sedating agents, including, but not limited to, benzodiazepines, non-benzodiazepine anxiolytics/hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, or monocarboxylate transporter (MCT) inhibitors, e.g. diclofenac, valproate, ibuprofen, within 2 weeks prior to enrollment (discontinuation for the purpose of study enrollment is permitted only if considered safe by the Investigator and approved by the Medical Monitor).
18. Treatment with an antidepressant for cataplexy, if the withdrawal of the antidepressant during cross-titration with JZP-258 might be unsafe due to prior history of depression.
19. Current treatment with oral isotretinoin.
20. Received any investigational drug within 30 days or 5 half-lives (whichever is longer) before the Screening Visit.
21. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation or placebo.
22. Unsafe for the subject to receive placebo treatment for 2 weeks, in the opinion of the Investigator.

8.1.6 Concomitant Medications

Not specified other than the above.

8.1.7 Schedule

The schedule for the main study is below.

	Screen- ing		Optimized Treatment and Titration									Stable- Dose Period	DB Randomized- Withdrawal Period		Safety Follow- up Period
Events	Study Entry	Switch to or Start JZP-258	Begin Titration ¹									End Titration Begin Stable-Dose	End of Stable-Dose Begin DB Treatment	End of DB Treatment or Early Termination	
Visits ² Phone contacts are shaded except for Wk 1 (see footnote)	V1	V2	V3 Clinic Visit Call ⁵	V4 V5 Call	V6	V7 V8 V9 Call	V10	V11 Call	V12 Call	V13 Call	V14	V15	V16	V17	
End of Week (W)	Day -30 to -1	Day 1	(+ 3 days)									(+ 3 days)	(+ 3 days)	(+ 3 days)	(+ 3 days)
Instruct subject on discontinuation of excluded medications	X		W1	W2, W3	W4	W5, W6, W7	W8	W9	W10	W11	W12	W14	W16	W18	
Cataplexy Frequency Diary		X	X ³	X	X	X	X	X	X	X	X	X	X	X	
Review/discuss subject diaries for completeness			X ⁵	X	X	X	X	X	X	X	X	X	X	X	
Assess control of cataplexy, EDS and tolerability to current dose.			X ⁵	X	X	X	X	X	X	X	X				
ESS												X	X		
PGIc narcolepsy overall ⁶													X	X	
CGIc narcolepsy overall												X			
CGIc narcolepsy overall ⁶													X	X	
SF-36												X	X		
EuroQoL												X	X		
C-SSRS Screening/Baseline Version	X														
C-SSRS Since Last Visit Version		X	X		X		X				X	X	X	X	
PHQ-9	X	X		X (W2 only)	X	X (W6 only)	X		X		X	X	X	X	
AE Reporting		X	X ³	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X ⁵	X	X	X	X	X	X	X	X	X	X	X	

	Screen- ing		Optimized Treatment and Titration										Stable- Dose Period	DB Randomized- Withdrawal Period		Safety Follow- up Period
Events	Study Entry	Switch to or Start JZP-258	Begin Titration ¹										End Titration Begin Stable-Dose	End of Stable-Dose Begin DB Treatment	End of DB Treatment or Early Termination	
Visits ² Phone contacts are shaded except for Wk 1 (see footnote)	V1	V2	V3 Clinic Visit Call ⁵	V4 V5 Call	V6	V7 V8 V9 Call	V10	V11 Call	V12 Call	V13 Call		V14	V15	V16	V17	
End of Week (W)	Day -30 to -1	Day 1	(+ 3 days)										(+ 3 days)	(+ 3 days)	(+ 3 days)	(+ 3 days)
			W1	W2, W3	W4	W5, W6, W7	W8	W9	W10	W11		W12	W14	W16	W18	
Groups 1 and 2: Switch Xyrem to JZP-258 and maintain dose for 2 weeks		X	X ⁵													
Groups 3 and 4: Initiate JZP-258 and titrate over a minimum of 2 weeks		X	X													
Groups 2 and 3: Taper off anticataplectic over a minimum of 2 weeks				X	X	X	X	X								
Groups 2 and 3: Confirm taper completed and no anticataplectic use									X	X						
All Groups: Further titration of JZP-258 as necessary				X	X	X	X	X								
All Groups: Maintain JZP-258 at stable dose (Wks 10-12)									X	X						
Randomize subjects													X			
All Groups: Dose with DB study drug (Wks 14-16)													X	X		
Study Drug Dosing Diary; assess diary for completeness and compliance after start of dosing		X ⁷	X ⁵	X	X	X	X	X	X	X		X	X	X		
Dispense Study Drug		X			X			X				X	X ⁸			
Collect study drug, measure compliance					X			X				X	X	X		



Shaded columns indicate phone contacts

- 1 All subjects will begin JZP-258 treatment at the beginning of this period and continue through Week 12. The subject must be maintained on a stable, tolerable and effective dose for at least 2 weeks, prior to entering the Stable-Dose Period.
 - 2 The Investigator may have the subject attend an unscheduled visit, at any time during the study, if deemed necessary.
 - 3 When necessary, a PSG may be performed, with the approval of the Jazz Pharmaceuticals Medical Monitor, to evaluate the subject for evidence of sleep disordered breathing, if the subject has not been adequately evaluated prior to study entry. A PSG and MSLT may also be performed, if necessary, with approval of the Jazz Pharmaceuticals' Medical Monitor for diagnosis of narcolepsy. The PSG and MSLT will be performed according to the study center's standard procedures.
 - 4 Electrolytes to include sodium (Na⁺), potassium (K⁺), magnesium (Mg²⁺), and calcium (Ca²⁺).
 - 5 At Week 1 subjects in Pre-randomization Groups 1 and 2 will have a phone contact for assessments unless the Investigator elects to assess the subject in the clinic. Only assessments labeled with this footnote will be conducted during the phone contact for Pre-randomization Groups 1 and 2. If these groups are seen in the clinic at Week 1 all assessments in the Week 1 column should be completed.
 - 6 PGIC and CGIC questionnaires are not applicable for subjects who terminate the study early prior to the Double-Blind Treatment Period.
 - 7 The subject is expected to start Study Drug Dosing Diary completion on the morning after the subject is dispensed study drug at Visit 2.
 - 8 If the pre-defined efficacy stopping rules are met and safety is adequately characterized at the time of the interim analysis, accompanied by DMC recommendation, enrollment and randomization to placebo may stop. All subjects would enter the Double-Blind Randomized Withdrawal Period on open-label JZP-258.
- AE = adverse event; BP = blood pressure; CGIC = Clinical Global Impression of Change; CGIs = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; EuroQoL = European quality of life; HR = heart rate; MSLT = multiple sleep latency test; PGIC = Patient Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; PSG = polysomnogram; RR = respiratory rate; SF-36 = 36-Item Short Form Survey Questionnaire; TSH = thyroid stimulating hormone; UA = urinalysis; V = Visit; W, Wk = Week.

8.1.8 Outcome Measures

8.1.8.1 Primary Efficacy Endpoint

Change in weekly number of cataplexy attacks from the 2-week stable dose period to the 2-week double-blind treatment period.

The frequency of cataplexy attacks was determined from a patient diary (Cataplexy Frequency Diary) recorded each night prior to bedtime: patients were asked to record the frequency of cataplexy attacks recorded each day.

8.1.8.2 Key Secondary Efficacy Endpoint

Change in Epworth Sleepiness Scale score from the 2-week stable dose period to the 2-week double-blind treatment period.

The Epworth Sleepiness Scale is a patient-rated measure of daytime sleepiness. Patients are asked to rate their chances of dozing during each of the following 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high): sitting and reading; watching TV, sitting inactive in a public place; as a passenger in a car for an hour without a break; lying down to rest in the afternoon when circumstances permit; sitting talking to someone; sitting quietly after a lunch without alcohol; in a car while stopped for a few minutes in traffic

8.1.8.3 Other Efficacy Endpoints

- Patient Global Impression of Change for narcolepsy overall.
- Clinical Global Impression of Change for narcolepsy overall.
- Change in quality of life based on Short Form-36.
- EuroQol 5 Dimensions Self-Report Questionnaire.

8.1.8.4 Safety Measures

Adverse events, vital signs, weight, physical examinations, 12-lead electrocardiogram, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and Columbia-Suicide Severity Rating Scale (for assessing suicidality). Patient Health Questionnaire-9.

8.1.9 Analysis Plan

8.1.9.1 Analysis Of Primary And Key Secondary Efficacy Endpoint

As already noted:

- The primary efficacy parameter was the change in weekly number of cataplexy attacks from the 2-week stable dose period to the 2-week double-blind treatment period.
- The key secondary efficacy parameter was the change in Epworth Sleepiness Scale score from the 2-week stable dose period to the 2-week double-blind treatment period.

A hierarchical sequential testing strategy was to be employed to analyze the primary and key secondary efficacy parameters, so as to control the familywise Type 1 error rate at the 0.05 level of significance (two-sided).

The sequential testing strategy was to begin by comparing JZP-258 with placebo for the primary efficacy parameter. If the comparison was statistically significant at the 0.05 level (two-sided), the treatment groups were then to be compared on the key secondary efficacy parameter at the 0.05 level (two-sided).

An analysis of covariance model was to be used to assess the primary efficacy parameter. The model was to include treatment group and pre-randomization group as fixed effects and the weekly number of cataplexy attacks during the stable dose period as a covariate. The estimate for the treatment difference and its 95% confidence intervals were to be presented. The normality assumptions of the model were to be examined by residual analysis. If the normality assumption was considered violated, a non-parametric analysis of covariance with the data replaced by ranks was to be used.

The key secondary efficacy parameter was to be analyzed in a manner similar to the primary efficacy parameter.

8.1.9.2 Analysis Of Other Secondary Efficacy Endpoints

Ordinal categorical parameters were to be analyzed using the Cochran-Mantel-Haenszel test for the row mean score difference. Other non-categorical parameters were to be analyzed by analysis of covariance or non-parametric analysis of covariance similar to the primary efficacy analysis.

8.1.9.3 Safety Analyses

Safety analyses were to be descriptive, and no formal statistical testing was to be performed.

8.1.9.4 Sample Size Estimate

A sample size of 65 subjects randomized per treatment group was calculated to provide at least 90% power to detect a difference in the change in the mean weekly number of cataplexy attacks of 17.5 between the oxybate mixed-salt oral solution formulation and placebo groups, assuming a standard deviation of 30 and a significance level of 0.05 (two-sided) using a t-test. Assuming a 30% dropout rate prior to randomization, 185 patients were to be enrolled so that at least 130 patients enter the double-blind treatment period.

8.2 Study Results

The study appears to have been conducted in a manner consistent with the last version of the clinical protocol.

8.2.1 Patient Disposition

255 patients were screened, of whom 201 patients were enrolled in the study.

Of the 201 patients enrolled in the study:

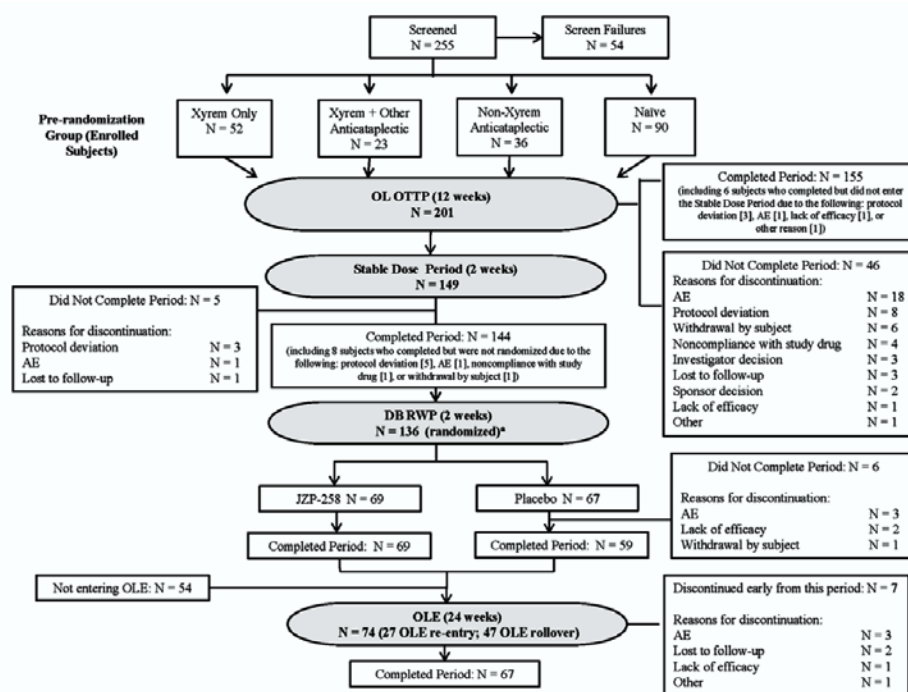
- 52 patients were receiving Xyrem only.
- 23 patients were receiving a combination of Xyrem and another (unapproved) anti-cataplectic drug.
- 36 patients were on a non-Xyrem (unapproved) anti-cataplectic drug.
- 90 patients were drug-naïve at study entry.

All 201 patients entered the main study in the optimized treatment and titration period (12 weeks). 155 patients completed that period, of whom 149 patients entered the stable-dose period (2 weeks). 144 out of 149 patients completed the stable-dose period.

136 out of 144 patients who completed the stable-dose period were then randomized, entering the randomized, double-blind, placebo-controlled, withdrawal period (2 weeks). At the beginning of that period, 69 patients were randomized to JZP-258 and 67 patients were randomized to placebo; all 69 patients randomized to JZP-258 and all 59 patients randomized to placebo completed the study.

74 patients then entered the open-label extension study; 67 patients completed that part of the study.

The above data and the reasons why patients did not complete each period of the study are summarized in the following table which I have copied from the submission.



Abbreviations: AE = adverse event; DB RWP = Double-blind Randomized-withdrawal Period; OLE = Open-label Extension; OL OTP = open-label Optimized Treatment and Titration Period. For OLE re-entry subjects, there was a variable gap between completion of Main Study and re-entry for OLE due to availability of approved Protocol Amendment 4.
* Subjects (b) (6) and (b) (6) were randomized in error and did not take study drug in the DB RWP.

8.2.2 Analysis Populations

Analysis populations for the double-blind randomized withdrawal period (based on the all randomized subjects population) are summarized in the following table, which I have copied from the submission. The table is self-explanatory. Note that 134 out of 136 patients randomized were included in the population for efficacy analysis.

	Treatment Group		Total (N = 136) n (%)
	JZP-258 (N = 69) n (%)	Placebo (N = 67) n (%)	
Analysis Population			
Safety Population	69 (100.0)	65 (97.0)	134 (98.5)
Excluded from this analysis population ^a	0	2 (3.0)	2 (1.5)
Efficacy Population	69 (100.0)	65 (97.0)	134 (98.5)
Excluded from this analysis population ^a	0	2 (3.0)	2 (1.5)
Reason for exclusion ^{b,c}			
Did not receive any double-blind study drug	0	2 (100.0)	2 (100.0)
Per-protocol Population	68 (98.6)	63 (94.0)	131 (96.3)
Excluded from this analysis population ^a	1 (1.4)	4 (6.0)	5 (3.7)
Reason for exclusion ^{b,c}			
Excluded from the Efficacy Population	0	2 (50.0)	2 (40.0)
Had at least 1 major protocol deviation potentially having an impact on efficacy data ^{b,d}	1 (100.0)	2 (50.0)	3 (60.0)
Concomitant medications	1 (100.0)	1 (50.0)	2 (66.7)
Laboratory assessments	0	1 (50.0)	1 (33.3)

^a Percentages were based on the number of subjects who entered the period.

^b A subject could have been reported in more than 1 reason for exclusion.

^c Percentages were based on the number of subjects who were excluded from this analysis population reported in each column.

^d Percentages were based on the number of subjects with at least 1 major protocol deviation potentially having an impact on efficacy data reported in each column.

8.2.3 Demographic And Other Baseline Characteristics (Efficacy Population)

These are summarized in the next sponsor table. As the table indicates, the two treatment groups were comparable in regard to the most significant parameters.

Characteristic (unit) Category	Treatment Group		Total (N=134)
	JZP-258 (N=69)	Placebo (N=65)	
Age (years)			
N	69	65	134
Mean	37.2	37.8	37.5
SD	11.79	12.69	12.19
Median	39.0	35.0	38.0
Min, Max	18, 68	18, 70	18, 70
Sex, n (%)			
Male	26 (37.7)	26 (40.0)	52 (38.8)
Female	43 (62.3)	39 (60.0)	82 (61.2)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	3 (4.3)	4 (6.2)	7 (5.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	64 (92.8)	59 (90.8)	123 (91.8)
Not reported	1 (1.4)	2 (3.1)	3 (2.2)
Multiple ^a	1 (1.4)	0	1 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	8 (11.6)	6 (9.2)	14 (10.4)
Not Hispanic or Latino	58 (84.1)	56 (86.2)	114 (85.1)
Not reported	3 (4.3)	2 (3.1)	5 (3.7)
Unknown	0	0	0

Characteristic (unit) Category	Treatment Group		Total (N=134)
	JZP-258 (N=69)	Placebo (N=65)	
Missing	0	1 (1.5)	1 (0.7)
BMI (kg/m ²) at baseline			
N	68	65	133
Mean	27.266	29.944	28.575
SD	4.9889	6.0319	5.6640
Median	26.430	28.870	28.000
Min, Max	19.09, 40.56	20.68, 47.88	19.09, 47.88
n missing	1	0	1
Childbearing potential, n (%)			
Yes	35 (50.7)	27 (41.5)	62 (46.3)
No	8 (11.6)	12 (18.5)	20 (14.9)
Not Applicable	26 (37.7)	26 (40.0)	52 (38.8)
Dosing information at randomization, n (%)			
Unequal nighttime JZP-258 Dosages	7 (10.1)	3 (4.6)	10 (7.5)
Equal nighttime JZP-258 Dosages	62 (89.9)	62 (95.4)	124 (92.5)
Twice nightly JZP-258	68 (98.6)	65 (100.0)	133 (99.3)
Thrice nightly JZP-258	1 (1.4)	0	1 (0.7)
Region, n (%)			
North America	23 (33.3)	23 (35.4)	46 (34.3)
Europe	46 (66.7)	42 (64.6)	88 (65.7)

BMI = body mass index; DB RWP = Double-blind Randomized-withdrawal Period; Max = maximum; Min = minimum;
SD = standard deviation

^a Subjects who reported > 1 race.

Baseline was defined as the last non-missing assessment collected prior to or on the same day as the first dose of study drug, including unscheduled assessments.

Dosing information at randomization was defined as the latest dosing information prior to randomization to the DB RWP treatment.

Age, in years, was calculated based on the date of signed informed consent for the Main Study. If the date of birth was missing, the age corresponds to the age collected by the sites.

Percentages were based on the total number of subjects in the analysis population reported in each column (N).

8.2.4 Disease History

Disease history comparisons for the two treatment groups in the efficacy population are in the sponsor table below.

Disease Characteristic	Treatment Group		Total (N = 134)
	JZP-258 (N = 69)	Placebo (N = 65)	
Time since diagnosis (years)			
N	69	65	134
Mean	8.40	6.83	7.64
SD	8.460	5.629	7.243
Median	5.55	5.75	5.65
Min, Max	0.1, 39.3	0.0, 21.0	0.0, 39.3
Past symptoms of narcolepsy experienced prior to any narcolepsy treatment, n (%) ^a			
Cataplexy	69 (100.0)	65 (100.0)	134 (100.0)
EDS	69 (100.0)	65 (100.0)	134 (100.0)
Hypnagogic and/or hypnopompic hallucinations	38 (55.1)	42 (64.6)	80 (59.7)
Sleep paralysis	41 (59.4)	42 (64.6)	83 (61.9)
Disrupted nighttime sleep	43 (62.3)	44 (67.7)	87 (64.9)
Current symptoms of narcolepsy, n (%) ^a			
Cataplexy	66 (95.7)	60 (92.3)	126 (94.0)
EDS	67 (97.1)	63 (96.9)	130 (97.0)
Hypnagogic and/or hypnopompic hallucinations	27 (39.1)	27 (41.5)	54 (40.3)
Sleep paralysis	29 (42.0)	23 (35.4)	52 (38.8)
Disrupted nighttime sleep	40 (58.0)	37 (56.9)	77 (57.5)
Unequal nighttime Xyrem dosages at study entry, n (%)	2 (2.9)	3 (4.6)	5 (3.7)
Equal nighttime Xyrem dosages at study entry, n (%)	26 (37.7)	24 (36.9)	50 (37.3)
Twice nightly Xyrem at study entry, n (%)	25 (36.2)	24 (36.9)	49 (36.6)
Thrice nightly Xyrem at study entry, n(%)	1 (1.4)	0	1 (0.7)

EDS = excessive daytime sleepiness; Max = maximum; Min = minimum; SD = standard deviation

^a Subject could have been included in > 1 category.

Time since diagnosis, in years, was calculated based on the date of signed informed consent.

Percentages were based on the total number of subjects in the analysis population reported in each column (N).

Partial diagnosis date was assigned for calculations as earliest possible date (ie, first day of month if day unknown or 01 January if day and month were unknown).

8.2.5 Treatment Compliance

Treatment compliance in all 4 pre-randomization groups was high across the main study, including the stable-dose period, as depicted in the following sponsor table.

Please also note that the term “pre-randomization group” is used by the sponsor to define the categories to which patients belonged at the time of study entry. The only point in the course of the study during which randomization actually occurred was at the start of the two randomized, double-blind, placebo-controlled, withdrawal segment.

Study Period Treatment Group ^a	Pre-randomization Group				Total (N = 201)
	Xyrem Only (N = 52)	Xyrem + Other Anticatataplectic (N = 23)	Non-Xyrem Anticatataplectic (N = 36)	Naïve (N = 90)	
Across All Study Periods					
n	52	23	36	90	201
Mean (SD)	86.52 (22.911)	91.60 (21.990)	93.19 (19.059)	85.47 (21.398)	87.83 (21.543)
Median	93.40	97.20	95.80	89.60	94.70
Min, Max	0.0, 143.1	0.0, 111.1	43.9, 148.1	22.6, 166.7	0.0, 166.7
Compliance rate, n (%)					
< 75%	11 (21.2)	2 (8.7)	5 (13.9)	20 (22.2)	38 (18.9)
75 to 125%	40 (76.9)	21 (91.3)	29 (80.6)	69 (76.7)	159 (79.1)
> 125%	1 (1.9)	0	2 (5.6)	1 (1.1)	4 (2.0)
OL OTTP					
n	52	23	36	90	201
Mean (SD)	89.41 (22.208)	92.40 (22.382)	96.93 (18.193)	92.43 (19.443)	92.45 (20.323)
Median	97.95	97.80	98.65	96.90	97.80
Min, Max	0.0, 109.2	0.0, 111.1	43.9, 148.1	26.6, 166.7	0.0, 166.7
Compliance rate, n (%)					
< 75%	8 (15.4)	2 (8.7)	4 (11.1)	8 (8.9)	22 (10.9)
75 to 125%	44 (84.6)	21 (91.3)	30 (83.3)	81 (90.0)	176 (87.6)
> 125%	0	0	2 (5.6)	1 (1.1)	3 (1.5)
Stable Dose Period					
n	44	14	23	65	146
Mean (SD)	96.46 (9.002)	97.43 (5.767)	92.10 (7.781)	95.30 (15.191)	95.35 (11.855)
Median	97.10	100.00	94.20	96.50	96.30
Min, Max	68.6, 125.0	88.2, 104.2	75.4, 104.2	0.0, 133.3	0.0, 133.3
Compliance rate, n (%)					
< 75%	2 (4.4)	0	0	2 (3.0)	4 (2.7)
75 to 125%	42 (95.5)	14 (100.0)	23 (100.0)	62 (95.4)	141 (96.6)
> 125%	0	0	0	1 (1.5)	1 (0.7)
DB RWP					
JZP-258 (N = 69)					
n	22	6	11	30	69
Mean (SD)	96.17 (14.112)	100.95 (1.043)	95.35 (7.153)	99.27 (9.286)	97.80 (10.466)
Median	98.05	101.20	94.40	96.80	98.00
Min, Max	42.9, 116.7	99.4, 102.0	83.3, 109.0	82.4, 129.6	42.9, 129.6
Compliance rate, n (%)					

Study Period Treatment Group ^a	Pre-randomization Group				Total (N = 201)
	Xyrem Only (N = 52)	Xyrem + Other Anticatataplectic (N = 23)	Non-Xyrem Anticatataplectic (N = 36)	Naïve (N = 90)	
< 75%	1 (4.5)	0	0	0	1 (1.4)
75 to 125%	21 (95.5)	6 (100.0)	11 (100.0)	29 (96.7)	67 (97.1)
> 125%	0	0	0	1 (3.3)	1 (1.4)
Placebo (N = 65)					
n	19	8	10	28	65
Mean (SD)	102.61 (13.255)	103.88 (6.441)	99.10 (14.172)	96.61 (8.545)	99.64 (11.042)
Median	100.00	104.00	98.90	96.25	99.70
Min, Max	76.2, 138.9	92.6, 112.2	81.5, 129.6	78.1, 115.1	76.2, 138.9
Compliance rate, n (%)					
< 75%	0	0	0	0	0
75 to 125%	18 (94.7)	8 (100.0)	9 (90.0)	28 (100.0)	63 (96.9)
> 125%	1 (5.3)	0	1 (10.0)	0	2 (3.1)
Total (N = 134)					
n	41	14	21	58	134
Mean (SD)	99.15 (13.936)	102.62 (5.001)	97.14 (10.938)	97.99 (8.958)	98.69 (10.748)
Median	98.20	101.55	97.00	96.30	98.15
Min, Max	42.9, 138.9	92.6, 112.2	81.5, 129.6	78.1, 129.6	42.9, 138.9
Compliance rate, n (%)					
< 75%	1 (2.4)	0	0	0	1 (0.7)
75 to 125%	39 (95.1)	14 (100.0)	20 (95.2)	57 (98.3)	130 (97.0)
> 125%	1 (2.4)	0	1 (4.8)	1 (1.7)	3 (2.2)
OLE					
n	14	2	11	30	57
Mean (SD)	86.26 (30.227)	79.70 (23.617)	73.47 (15.931)	76.21 (20.822)	78.27 (22.688)
Median	87.45	79.70	77.80	75.95	79.10
Min, Max	48.7, 168.7	63.0, 96.4	49.9, 95.4	33.8, 103.5	33.8, 168.7
Compliance rate, n (%)					
< 75%	5 (35.7)	1 (50.0)	5 (45.5)	14 (46.7)	25 (43.9)
75 to 125%	8 (57.1)	1 (50.0)	6 (54.5)	16 (53.3)	31 (54.4)
> 125%	1 (7.1)	0	0	0	1 (1.8)

DB RWP = Double-blind Randomized-withdrawal Period; Max = maximum; Min = minimum; OLE = Open-label Extension;
OL OTTP = open-label Optimized Treatment and Titration Period; SD = standard deviation

^a Only for the DB RWP.

Compliance with study drug, in percentage, was calculated as follows: volume of solution taken during the study period (ie, total dispensed – total returned) divided by the volume of solution that should have been taken by the subject during the study period and then, multiply by 100%.

Percentages were based on the total number of subjects dosed in the analysis population for each period who returned bottles.

8.2.6 Efficacy Results

8.2.6.1 Primary Efficacy Analysis

The primary efficacy analysis compared the JZP-258 and placebo groups on the change in weekly frequency of all cataplexy attacks from baseline (the 2 weeks

of the stable dose period) over the randomized, double-blind, placebo-controlled, withdrawal period.

The results of the primary efficacy analysis are in the next sponsor table. As the table indicates, a statistically significant superiority of JZP-258 over placebo was seen on this measure, with a greater increase in cataplexy frequency in those administered placebo than in those continuing JZP-258 during the randomized, double-blind, placebo-controlled withdrawal period.

Average Weekly Number of Cataplexy Attacks	JZP-258 (N = 69)	Placebo (N = 65)
Baseline (2 weeks of the Stable Dose Period)		
n	69	65
Mean (SD)	8.91 (16.829)	7.16 (14.412)
Median	1.08	1.00
Q1, Q3	0.00, 7.88	0.00, 4.45
2 weeks of the DB RWP		
n	69	65
Mean (SD)	9.03 (16.927)	18.63 (32.745)
Median	2.15	5.44
Q1, Q3	0.00, 10.50	1.50, 16.69
Change from baseline (2 weeks of the Stable Dose Period) to the 2 weeks of the DB RWP		
n	69	65
Mean (SD)	0.12 (5.772)	11.46 (24.751)
Median	0.00	2.35
Q1, Q3	-0.49, 1.75	0.00, 11.61
Location shift ^a		-3.308
95% CI ^a		(-6.044, -1.500)
p-value ^b		<0.0001

ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; CI = confidence interval;

DB RWP = Double-blind Randomized-withdrawal Period; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

^a The location shift between 2 treatment groups and asymptotic 95% CI were from Hodges-Lehmann estimate (JZP-258 – placebo).

^b The p-value was obtained from a rank-based ANCOVA model including the change in average weekly number of cataplexy attacks from the 2 weeks of the Stable Dose Period to the 2 weeks of the DB RWP as response variable, pre-randomization group and treatment group as fixed effects; and average weekly number of cataplexy attacks during the 2 weeks of the Stable Dose Period as covariate.

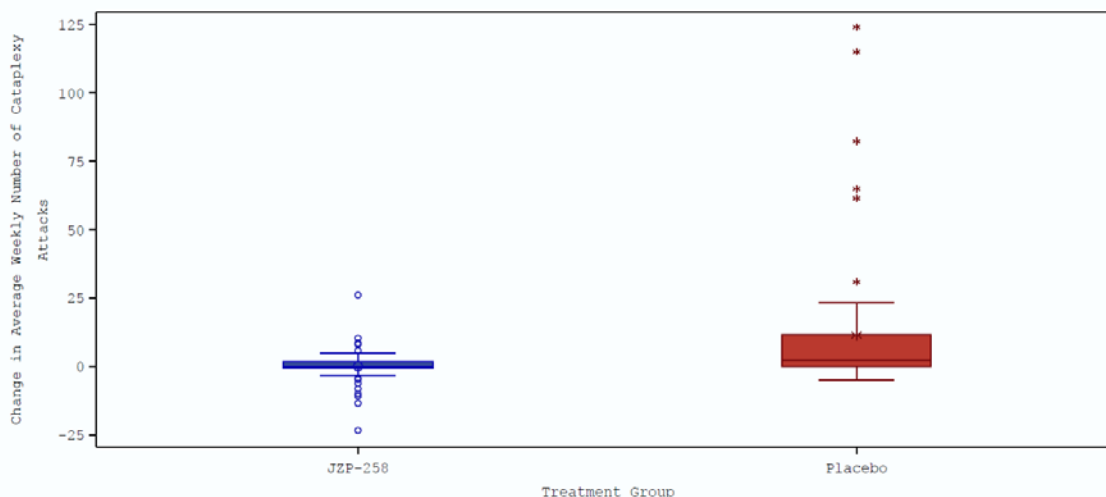
For subjects with at least 1 day of cataplexy attacks diary, the average weekly number of cataplexy attacks by week was calculated as follows: total number of cataplexy attacks within the week divided by the number of days with non-missing data within the week and then, multiplied by 7 days; and the average weekly number of cataplexy attacks by study period was calculated as follows: total number of cataplexy attacks within the 2 weeks period divided by the number of days with non-missing data within the 2 weeks period and then, multiplied by 7 days.

For subjects without post randomization daily cataplexy attack data, the result from the Stable Dose Period was carried forward using a BOCF approach.

For the DB RWP, Week 1 and Week 2 were based on the observed data. Baseline observation carried forward imputed data was used for the 2 weeks of the study period and change from the 2 weeks of the study period.

Shapiro-Wilk normality test for residual was significant at alpha level of 0.05.

The box plot for the above data is depicted below.



IQR = interquartile range

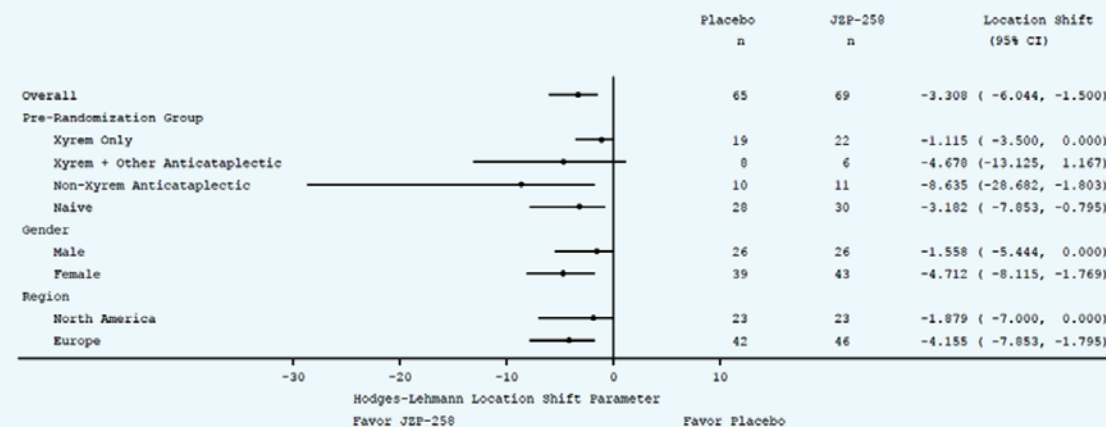
The average weekly number of cataplexy attacks by study period was calculated as follows: total number of cataplexy attacks within the 2-week period divided by the number of days with non-missing data within the 2-weeks period, and then multiplied by 7 days. For subjects without post randomization daily cataplexy attack data, the result from the Stable Dose Period was carried forward using a baseline observation carried forward approach.

The bottom and top edges of the box indicate the first and third quartiles (the difference is the IQR), the line inside the box is the median, and the marker inside the box is the mean. Any points that are a distance of more than 1.5*IQR from the box are considered outliers and are represented as a ^o. The whiskers that extend from the box indicate the minimum and maximum after removing those outliers.

Similar results were observed during two sensitivity analysis: an analysis conducted on the per-protocol population, and an analysis conducted on the efficacy population using the last-observation-carried-forward method.

Similar trends were also observed in subgroups defined by pre-randomization groups, sex, and region as indicated by the following sponsor figure.

Forest Plot of Change in Average Weekly Number of Cataplexy Attacks from the 2 Weeks of the Stable Dose Period to the 2 Weeks of the Double-Blind Randomized-Withdrawal Period by Subgroups (Efficacy Population)



CI = confidence interval

The average weekly number of cataplexy attacks by study period was calculated as follows: total number of cataplexy attacks within the 2-week period divided by the number of days with non-missing data within the 2-week period and then multiplied by 7 days. For subjects without post randomization daily cataplexy attack data, the result from the Stable Dose Period was carried forward using a baseline observation carried forward approach.

8.2.6.2 Analysis Of Key Secondary Efficacy Endpoint

The analysis of the key secondary efficacy endpoint compared the JZP-258 and placebo groups on the change in Epworth Sleepiness Scale score from baseline (the end of the 2-week stable dose period) to the end of the randomized, double-blind, placebo-controlled, withdrawal period.

The results of the analysis of the key secondary efficacy endpoint are in the next sponsor table. As the table indicates, a statistically significant superiority of JZP-258 over placebo was seen on this measure, with a greater increase in Epworth Sleepiness Scale score in those administered placebo than in those continuing JZP-258 during the randomized, double-blind, placebo-controlled withdrawal period.

Timepoint	JZP-258 (N = 69)	Placebo (N = 65)
End of the Stable Dose Period		
n	69	65
Mean (SD)	13.6 (5.25)	12.6 (5.46)
Median	14.0	13.0
Q1, Q3	10.0, 19.0	9.0, 17.0
End of the DB RWP		
N	69	65
Mean (SD)	13.6 (4.66)	15.6 (4.88)
Median	14.0	16.0
Q1, Q3	10.0, 17.0	13.0, 19.0
Change from End of Stable Dose Period to End of DB RWP		
n	69	65
Mean (SD)	0.0 (2.90)	3.0 (4.68)
Median	0.0	2.0
Q1, Q3	-1.0, 1.0	0.0, 5.0
Location shift ^a		-2.00
95% CI ^a		(-4.00, -1.00)
p-value ^b		< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; DB RWP = Double-blind Randomized-withdrawal Period; ESS = Epworth Sleepiness Scale; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

^a The location shift between 2 treatment groups and asymptotic 95% CI were from Hodges-Lehmann estimate (JZP-258 - placebo).

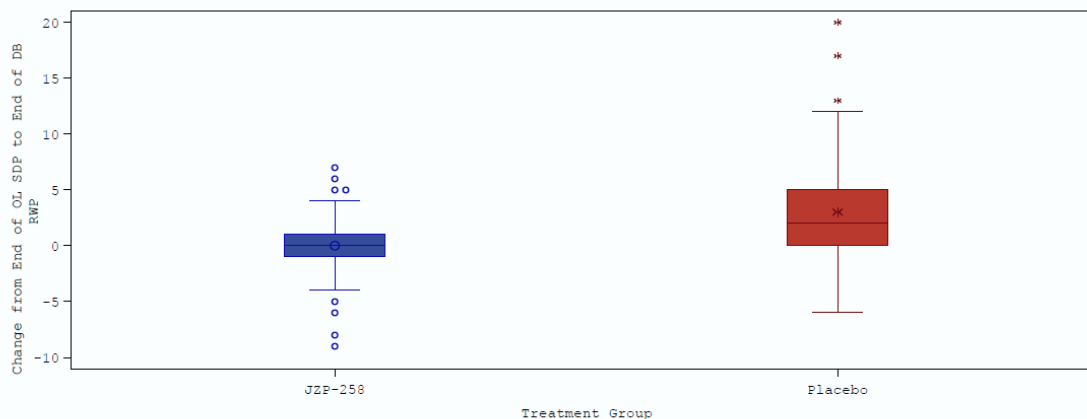
^b The p-value was obtained from a rank-based ANCOVA model including the change in ESS total score from the end of the Stable Dose Period to the end of the DB RWP as response variable, pre-randomization group and treatment group as fixed effects, and ESS total score at the end of the Stable Dose Period (baseline) as covariate.

The ESS total score is the sum of the 8 item-scores and can range between 0 to 24. Higher scores indicate greater daytime sleepiness. If 3 or more item-scores were missing, the ESS total score was set to missing. If 1 or 2 ESS item-scores were missing at a specific time point, the mean of the remaining 7 or 6 non-missing ESS item-scores at that time point was used to impute the missing ESS item-scores. The ESS total score was then calculated as the sum of the observed and imputed item-scores.

For subjects without post randomization ESS total score data, the ESS total score from the Stable Dose Period was carried forward using a baseline (ie, assessment performed at the end of the Stable Dose Period) observation carried forward approach.

Shapiro-Wilk normality test for residual was significant at alpha level of 0.05.

The box plot for the above data is depicted below.

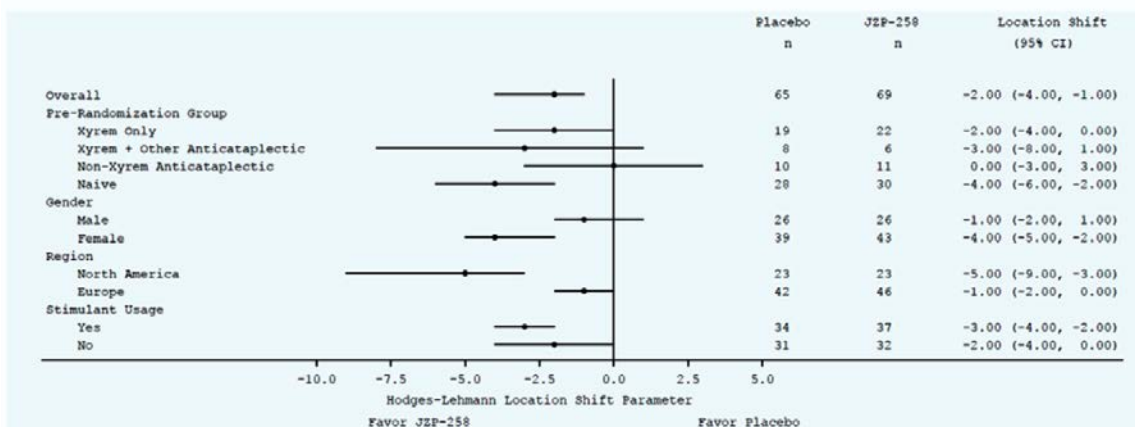


DB RWP = Double-blind Randomized-withdrawal Period; ESS = Epworth Sleepiness Scale; IQR = interquartile range;
OL SDP = Open-label Stable Dose Period

The ESS total score is the sum of the 8 item-scores and can range between 0 to 24. Higher scores indicate greater daytime sleepiness. If 3 or more item-scores were missing, the ESS total score was set to missing. If 1 or 2 ESS item-scores were missing at a specific time point, the mean of the remaining 7 or 6 non-missing ESS item-scores at that time point was used to impute the missing ESS item-scores. The ESS total score was then calculated as the sum of the observed and imputed item-scores. For subjects without post randomization ESS total score data, the ESS total score from the Stable Dose Period was carried forward using a baseline (ie, assessment performed at the end of the Stable Dose Period) observation carried forward approach. The bottom and top edges of the box indicate the first and third quartiles (the difference is the IQR), the line inside the box is the median, and the marker inside the box is the mean. Any points that are a distance of more than 1.5*IQR from the box are considered outliers and are represented as a '*'. The whiskers that extend from the box indicate the minimum and maximum after removing those outliers.

Similar trends were also observed in subgroups defined by pre-randomization groups, sex, region, and stimulant usage as indicated by the following sponsor figure.

Forest Plot of Change in ESS Total Score from the End of the Stable Dose Period to the End of the Double-Blind Randomized-Withdrawal Period by Subgroups (Efficacy Population)



CI = confidence interval; ESS = Epworth Sleepiness Scale

The ESS total score is the sum of the 8 item-scores and can range between 0 to 24. Higher scores indicate greater daytime sleepiness. If 3 or more item-scores were missing, the ESS total score was set to missing. If 1 or 2 ESS item-scores were missing at a specific time point, the mean of the remaining 7 or 6 non-missing ESS item-scores at that time point was used to impute the missing ESS item-scores. The ESS total score was then calculated as the sum of the observed and imputed item-scores. For subjects without post randomization ESS total score data, the ESS total score from the Stable Dose Period was carried forward using a baseline (ie, assessment performed at the end of the Stable Dose Period) observation carried forward approach.

8.2.6.3 Analysis Of Other Secondary Efficacy Endpoints

The results of the analysis of several other secondary efficacy endpoints are summarized below. The results of those analyses are self-explanatory.

The results of the analysis of the Clinical Global Impression of Change for Narcolepsy Overall at the end of the double-blind randomized withdrawal period (for the efficacy population) are in the sponsor table below.

Variable Category	JZP-258 (N = 69) n (%)	Placebo (N = 65) n (%)
CGIs for narcolepsy overall at the end of the Stable Dose Period^a		
Number of subjects with at least 1 CGIs survey, n	68	64
Normal; no signs of illness	0 (0.0)	1 (1.6)
Borderline ill	12 (17.6)	11 (17.2)
Slightly ill	20 (29.4)	20 (31.3)
Moderately ill	30 (44.1)	21 (32.8)
Markedly ill	4 (5.9)	10 (15.6)
Severely ill	2 (2.9)	1 (1.6)
Among the most extremely ill	0 (0.0)	0 (0.0)
CGIc for narcolepsy overall at the end of the DB RWP^b		
Number of subjects with at least 1 CGIc survey, n	68	65
Very much improved	1 (1.5)	0 (0.0)
Much improved	12 (17.6)	0 (0.0)
Minimally improved	9 (13.2)	3 (4.6)
No change	34 (50.0)	11 (16.9)
Minimally worse	8 (11.8)	12 (18.5)
Much worse	4 (5.9)	28 (43.1)
Very much worse	0 (0.0)	11 (16.9)
p-value ^c	< 0.0001	

CGIc = Clinical Global Impression of change; CGIs = Clinical Global Impression of severity; DB RWP = Double-blind Randomized-withdrawal Period

^a At the end of the Stable Dose Period, the investigator rated his/her impression of the severity of the subject's narcolepsy overall relative to his/her experience with this patient population.

^b At the end of the DB RWP/ early termination visit, the investigator rated their impression of any change in the severity of the subject's narcolepsy overall since the start of the DB RWP.

^c The p-value for the CGIc for narcolepsy overall at the end of the DB RWP is from a Cochran-Mantel-Haenszel row means score test.

Percentages are based on the total number of subjects with at least 1 survey in each treatment column.

The results of the analysis of the Patient Global Impression of Change for Narcolepsy Overall (for the efficacy population) at the end of the double-blind randomized withdrawal period are in the sponsor table below.

Variable Category	JZP-258 (N = 69) n (%)	Placebo (N = 65) n (%)
Number of subjects with at least 1 PGIC survey, n	69	65
Very much better	1 (1.4)	1 (1.5)
Much better	12 (17.4)	1 (1.5)
A little better	6 (8.7)	3 (4.6)
No change	39 (56.5)	10 (15.4)
A little worse	8 (11.6)	21 (32.3)
Much worse	2 (2.9)	20 (30.8)
Very much worse	1 (1.4)	9 (13.8)
p-value	< 0.0001	

PGIC = Patient Global Impression of change

At the end of the Double-blind Randomized-withdrawal Period/early termination visit, subjects rated the change in their condition since the end of the Stable Dose Period.

The p-value for the PGIC for narcolepsy overall at the end of the Double-blind Randomized-withdrawal Period is from a Cochran-Mantel-Haenszel row means score test.

Percentages and p-values are based on the total number of subjects with at least 1 survey in each treatment column.

The results of the analysis of the change in Short Form-36 Version Component Summary Scores from the end of the stable-dose period to the end of the double-blind randomized-withdrawal period (for the efficacy population) are in the following table, which I have copied from the submission.

Overall Component Study Period	JZP-258 (N = 69)	Placebo (N = 65)
Physical Component Summary		
End of the Stable Dose Period		
n	67	65
Mean (SD)	51.99 (8.649)	49.96 (9.075)
Median	53.90	51.47
Q1, Q3	46.93, 58.32	44.01, 57.44
End of the DB RWP ^a		
n	69	65
Mean (SD)	52.21 (7.673)	48.71 (8.733)
Median	53.70	50.65
Q1, Q3	47.17, 58.60	43.19, 55.80
Change from the End of the Stable Dose Period to the End of the DB RWP ^a		
n	67	65
Mean (SD)	0.01 (4.176)	-1.26 (5.229)
Median	-0.03	-1.92
Q1, Q3	-2.07, 2.41	-3.46, 1.73
Location shift ^b		1.410
95% CI ^b		(-0.130, 2.810)
p-value ^c		0.0174
Mental Component Summary		
End of the Stable Dose Period		
n	67	65
Mean (SD)	45.22 (12.218)	48.06 (9.941)
Median	50.80	50.47
Q1, Q3	36.97, 54.91	44.37, 54.32
End of the DB RWP ^a		
n	69	65
Mean (SD)	46.80 (11.245)	46.04 (9.871)
Median	50.07	47.42
Q1, Q3	40.49, 55.39	40.19, 53.78
Change from the End of the Stable Dose Period to the End of the DB RWP ^a		
n	67	65
Mean (SD)	1.31 (6.561)	-2.02 (7.814)
Median	1.55	-1.92
Q1, Q3	-1.88, 3.78	-6.28, 1.34
LS mean ^c	0.355	-2.166
LS mean difference ^c		2.521
95% CI ^c		(0.206, 4.837)
p-value ^c		0.0331

ANCOVA = analysis of covariance; DB RWP = Double-blind Randomized-withdrawal Period; CI = confidence interval; LS = least squares; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SF-36v2 = 36-Item Short Form Health Survey Version 2

^a For subjects without post randomization scale data, the result from the Stable Dose Period was carried forward using a baseline (ie, assessment performed at the end of the Stable Dose Period) observation carried forward approach.

^b The location shift between 2 treatment groups and asymptotic 95% CI were from Hodges-Lehmann estimate.

^c The LS means, LS mean difference, 95% CI, and p-value were obtained from a rank-based ANCOVA model including the change in the overall component score from the end of the Stable Dose Period to the end of the DB RWP as response variable; pre-randomization group and treatment group as fixed effects; and overall component score at the end of the Stable Dose Period as covariate.

The SF-36v2 is a multipurpose, short-form health survey with 36 questions/items. It yields to 8 scale profile of function health and well-being scores and 2 overall component summary measures. For each overall component, higher scores represent better health. Subjects have completed the SF-36v2, with a 1-week recall period.

8.2.7 Safety Results

The safety data for Study 15-006 in the original application for this NDA (submitted and received on January 21, 2020) had a cut-off date of January 24, 2019. The remaining safety data for that study (i.e., its open-label extension) were submitted and received on April 16, 2020.

The safety data for Study 15-006 are summarized below: they include both the data submitted with the original submission of this NDA (dated January 21, 2020) and those in the 120-Day Safety Update (of April 16, 2020).

Please again note that the term “pre-randomization group” is used by the sponsor to define the 4 categories to which patients belonged at the time of study entry. However, the only point in the course of the study during which randomization actually occurred was at the start of the two randomized, double-blind, placebo-controlled, withdrawal segment.

Comparisons of safety data between the 4 pre-randomization groups designated by the sponsor are of limited utility given that these 4 groups were not derived from randomization.

8.2.7.1 Main Study

The term “main study” refers to all study periods other than the open-label extension.

8.2.7.1.1 Adverse Events

8.2.7.1.1.1 Overall Summary Of Adverse Events

An overall summary of adverse events that occurred during the main study in JZP-258-treated patients is in the sponsor table below which is self-explanatory. Adverse events that occurred during placebo treatment are excluded from the table.

Category	Pre-randomization Group				Total (N = 201) n (%)
	Xyrem Only (N = 52) n (%)	Xyrem + Other Anticatataplectic (N = 23) n (%)	Non-Xyrem Anticatataplectic (N = 36) n (%)	Naïve (N = 90) n (%)	
Any TEAEs	31 (59.6)	20 (87.0)	30 (83.3)	72 (80.0)	153 (76.1)
Any severe TEAEs	0	3 (13.0)	5 (13.9)	2 (2.2)	10 (5.0)
Any life-threatening TEAEs	0	0	0	0	0
Any fatal TEAEs	0	0	0	0	0
Any TEAEs related to study drug	9 (17.3)	7 (30.4)	18 (50.0)	51 (56.7)	85 (42.3)
Any AEs with an outcome of death	0	0	0	0	0
Any serious TEAEs	0	2 (8.7)	1 (2.8)	1 (1.1)	4 (2.0)
Any TEAEs leading to discontinuation of study drug	2 (3.8)	5 (21.7)	6 (16.7)	8 (8.9)	21 (10.4)

AE = adverse event; TEAE = treatment-emergent adverse event

Data collected while subjects randomized to placebo were on placebo during the DB RWP plus the minimum of up to 30 days after completion of the DB RWP or the start of the OLE are excluded from this summary.

TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of open-label study drug up to the last dose of study drug during the OL OTTP, Open-label Stable-Dose Period, DB RWP or Open-label Extension Period (whichever is the latest) + 30 days, excluding AEs that started or worsened in severity after the last dose of study drug during the DB RWP + 30 days, but before the first dose of the Open-label Extension Period for subjects re-entering into the study.

A Related AE was defined as an AE with a relationship to study drug of related/suspected to be related. Adverse events with a missing relationship to study drug have been classified as related.

Subjects reporting > 1 AE under a category have been counted only once within that category.

Percentages are based on the total number of subjects in the analysis population reported in each column.

8.2.7.1.1.2 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

8.2.7.1.1.2.1 Deaths

There were no deaths during the main study.

8.2.7.1.1.2.2 Serious Adverse Events

4 patients (2%) treated with JZP-258 experienced serious adverse events during the main study, as did 2 patients who received placebo during the randomized, double-blind withdrawal period.

The 4 patients who experienced serious adverse events while receiving JZP-258 were as follows.

1. A patient had an accidental overdose (she took a second dose of JZP-258 after forgetting that she taken her first), and then experienced a confusional state and visual hallucinations.
2. A patient who developed a peripheral facial paresis.
3. A patient who developed a proven viral cardiomyopathy (a myocarditis).
4. A patient who developed a bile duct stone.

The 2 patients who experienced serious adverse events while receiving placebo during the randomized withdrawal period were as follows.

1. A patient who developed influenza.
2. A patient who developed a marked increase in serum creatine kinase the day after completing the randomized withdrawal period and then exited the study in the setting of intense exercise.

I have read the narratives provided in this application for all the above serious adverse events, supplemented by individual Case Report Forms when needed. None of the events listed above merit a more detailed description in this review.

8.2.7.1.1.2.3 Discontinuations Due To Adverse Events

21 patients (10.4%) who received JZP-258 experienced discontinuations due to adverse events during the main study. These are summarized in the following sponsor table.

System Organ Class Preferred Term	Pre-Randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticatataplectic (N=23) n (%)	Non-Xyrem Anticatataplectic (N=36) n (%)	Naive (N=90) n (%)	
Number of Subjects with at Least One TEAE Leading to Discontinuation of Study Drug	2 (3.8)	5 (21.7)	6 (16.7)	8 (8.9)	21 (10.4)
Gastrointestinal disorders	0	0	1 (2.8)	2 (2.2)	3 (1.5)
Nausea	0	0	1 (2.8)	2 (2.2)	3 (1.5)
Vomiting	0	0	0	1 (1.1)	1 (0.5)
General disorders and administration site conditions	0	0	1 (2.8)	0	1 (0.5)
Fatigue	0	0	1 (2.8)	0	1 (0.5)
Hepatobiliary disorders	0	0	0	1 (1.1)	1 (0.5)
Bile duct stone	0	0	0	1 (1.1)	1 (0.5)
Infections and infestations	0	0	1 (2.8)	0	1 (0.5)
Viral cardiomyopathy	0	0	1 (2.8)	0	1 (0.5)
System Organ Class Preferred Term	Pre-Randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticatataplectic (N=23) n (%)	Non-Xyrem Anticatataplectic (N=36) n (%)	Naive (N=90) n (%)	
Metabolism and nutrition disorders	0	0	0	1 (1.1)	1 (0.5)
Decreased appetite	0	0	0	1 (1.1)	1 (0.5)
Musculoskeletal and connective tissue disorders	0	0	0	1 (1.1)	1 (0.5)
Pain in extremity	0	0	0	1 (1.1)	1 (0.5)
Nervous system disorders	2 (3.8)	4 (17.4)	3 (8.3)	2 (2.2)	11 (5.5)
Cataplexy	0	4 (17.4)	3 (8.3)	0	7 (3.5)
Headache	1 (1.9)	0	0	1 (1.1)	2 (1.0)
Cognitive disorder	1 (1.9)	0	0	0	1 (0.5)
Somnolence	0	0	0	1 (1.1)	1 (0.5)
System Organ Class Preferred Term	Pre-Randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticatataplectic (N=23) n (%)	Non-Xyrem Anticatataplectic (N=36) n (%)	Naive (N=90) n (%)	
Psychiatric disorders	0	1 (4.3)	2 (5.6)	4 (4.4)	7 (3.5)
Anxiety	0	0	0	2 (2.2)	2 (1.0)
Depressed mood	0	0	1 (2.8)	1 (1.1)	2 (1.0)
Depression	0	0	0	2 (2.2)	2 (1.0)
Irritability	0	0	0	2 (2.2)	2 (1.0)
Abnormal sleep-related event	0	0	1 (2.8)	0	1 (0.5)
Sleep talking	0	0	1 (2.8)	0	1 (0.5)
Sleep-related eating disorder	0	1 (4.3)	0	0	1 (0.5)

During the randomized withdrawal period, 5 patients who received placebo discontinued treatment (there were no discontinuations in those who continued to receive JZP-258 during that period). The adverse events seen in these patients included somnolence (3 patients), cataplexy (2 patients), insomnia (1 patient), sleep disorder (1 patient), and influenza (1 patient).

I have read the narratives provided in this application for all the above adverse events that led to treatment discontinuation, supplemented by individual Case Report Forms when needed. None of the events listed above warrant a more detailed description in this review.

8.2.7.1.1.3 Treatment-Emergent Adverse Events

The overall incidence of adverse events reported in $\geq 5\%$ of subjects in any pre-randomization treatment group, in the main study, and grouped by system organ class and Preferred Term is in the next sponsor table. Placebo-treated patients are excluded.

System Organ Class Preferred Term	Pre-randomization Group				Total (N = 201) n (%)
	Xyrem Only (N = 52) n (%)	Xyrem + Other Anticataplectic (N = 23) n (%)	Non-Xyrem Anticataplectic (N = 36) n (%)	Naïve (N = 90) n (%)	
Any TEAE	31 (59.6)	20 (87.0)	30 (83.3)	72 (80.0)	153 (76.1)
Cardiac Disorders	0	0	2 (5.6)	0	2 (1.0)
Palpitations	0	0	2 (5.6)	0	2 (1.0)
Gastrointestinal Disorders	9 (17.3)	3 (13.0)	10 (27.8)	23 (25.6)	45 (22.4)
Nausea	2 (3.8)	1 (4.3)	7 (19.4)	16 (17.8)	26 (12.9)
Diarrhoea	4 (7.7)	0	0	7 (7.8)	11 (5.5)
Vomiting	1 (1.9)	0	4 (11.1)	5 (5.6)	10 (5.0)
Dry mouth	1 (1.9)	1 (4.3)	3 (8.3)	3 (3.3)	8 (4.0)
General Disorders and Administration Site Conditions	4 (7.7)	2 (8.7)	8 (22.2)	9 (10.0)	23 (11.4)
Fatigue	1 (1.9)	0	4 (11.1)	2 (2.2)	7 (3.5)
Infections and Infestations	12 (23.1)	8 (34.8)	19 (52.8)	25 (27.8)	64 (31.8)
Nasopharyngitis	2 (3.8)	1 (4.3)	5 (13.9)	7 (7.8)	15 (7.5)
Influenza	5 (9.6)	3 (13.0)	3 (8.3)	3 (3.3)	14 (7.0)
Upper Respiratory Tract Infection	1 (1.9)	1 (4.3)	1 (2.8)	6 (6.7)	9 (4.5)
Urinary Tract Infection	0	0	3 (8.3)	3 (3.3)	6 (3.0)
Vaginal Infection	0	0	2 (5.6)	0	2 (1.0)
Injury, Poisoning and Procedural Complications	2 (3.8)	2 (8.7)	4 (11.1)	2 (2.2)	10 (5.0)
Contusion	0	0	2 (5.6)	0	2 (1.0)
Fall	0	0	2 (5.6)	0	2 (1.0)
Metabolism and Nutrition Disorders	1 (1.9)	1 (4.3)	2 (5.6)	16 (17.8)	20 (10.0)
Decreased Appetite	0	1 (4.3)	2 (5.6)	12 (13.3)	15 (7.5)

8.2.7.1.1.4 Adverse Events During Randomized Withdrawal Phase

8.2.7.1.1.4.1 Overall Summary Of Adverse Events

An overall summary of adverse events reported during the two-week randomized withdrawal period is in the next table, copied from this submission. As the table indicates, the incidence of all adverse events, serious adverse events, and adverse events leading to discontinuation were higher in the placebo group than in the Xywav group during that period.

Category	JZP-258 (N = 69) n (%)	Placebo (N = 65) n (%)	Total (N = 134) n (%)
Any TEAEs	13 (18.8)	22 (33.8)	35 (26.1)
Any severe TEAEs	1 (1.4)	3 (4.6)	4 (3.0)
Any life-threatening TEAEs	0	0	0
Any fatal TEAEs	0	0	0
Any study drug-related TEAEs	3 (4.3)	11 (16.9)	14 (10.4)
Any AEs with an outcome of death	0	0	0
Any serious TEAEs	0	2 (3.1)	2 (1.5)
Any TEAEs leading to discontinuation of study drug	0	5 (7.7)	5 (3.7)

AE = adverse event; OLE = Open-label Extension; SAE = serious adverse event; SOC = system organ class;

TEAE = treatment-emergent adverse event

Treatment-emergent AEs were defined as any AEs that started or worsened in severity on or after the first dose of double-blind study drug up to 1) the last dose of double-blind study drug + 30 days for subjects who did not enter the OLE, 2) the first dose of study drug during the OLE for subjects who rolled over into the OLE immediately after having completed the Main Study or 3) whichever occurred first between the following 2 timepoints for subjects who rolled over into the OLE after having re-entered into the study: last dose of double-blind study drug + 30 days or first dose of study drug during the OLE.

A related AE was defined as an AE with a relationship to study drug of "related/suspected to be related." Adverse events with a missing relationship to study drug were classified as related.

Subjects reporting > 1 AE under a category have been counted only once within that category.

Percentages were based on the total number of subjects in the analysis population reported in each column (N).

8.2.7.1.1.4.2 Serious Adverse Events

As already noted, 2 patients who experienced serious adverse events while receiving placebo during the randomized withdrawal period were as follows.

1. A patient who developed influenza.
2. A patient who developed a marked increase in serum creatine kinase the day after completing the randomized withdrawal period and then exited the study in the setting of intense exercise.

8.2.7.1.1.4.3 Adverse Events Leading To Treatment Discontinuation

These are summarized in the next sponsor table, and occurred in 5 patients, all in the placebo group.

System Organ Class Preferred Term	Treatment Group		Total (N=134) n (%)
	JZP-258 (N=69) n (%)	Placebo (N=65) n (%)	
Number of Subjects with at Least One TEAE Leading to Discontinuation of Study Drug	0	5 (7.7)	5 (3.7)
Infections and infestations	0	1 (1.5)	1 (0.7)
Influenza	0	1 (1.5)	1 (0.7)
Nervous system disorders	0	4 (6.2)	4 (3.0)
Somnolence	0	3 (4.6)	3 (2.2)
Cataplexy	0	2 (3.1)	2 (1.5)
Psychiatric disorders	0	2 (3.1)	2 (1.5)
Insomnia	0	1 (1.5)	1 (0.7)
Sleep disorder	0	1 (1.5)	1 (0.7)

AE: Adverse Event. TEAE: Treatment-Emergent Adverse Event.

Note: The Double-Blind Randomized-Withdrawal Safety population includes all subjects who received at least one dose of double-blind study drug.

Note: TEAEs are defined as any AEs that started or worsened in severity on or after the first dose of double-blind study drug up to 1) the last dose of double-blind study drug + 30 days for subjects who did not enter the Open-Label Extension, 2) the first dose of study drug during the open-Label Extension for subjects who rolled over into the Open-Label Extension immediately after having completed the Main Study or 3) whichever occur first between the following two timepoints for subjects who rolled over into the Open-Label Extension after having re-entered into the study: last dose of double-blind study drug + 30 days or first dose of study drug during the Open-Label Extension.

Note: AEs have been coded using the MedDRA dictionary, version 19.1.

Note: Subjects reporting an AE more than once within a system organ class/preferred term have been counted only once within that system organ class/preferred term.

Note: A subject can have more than one preferred term under a given system organ class.

Note: Percentages are based on the total number of subjects in the analysis population reported in each column (N).

8.2.7.1.1.4.4 Incidence Of Individual Adverse Events

Treatment-emergent adverse events in $\geq 2\%$ of subjects in either treatment group with an onset during the randomized, double-blind withdrawal period are summarized in the next table copied from the submission.

System Organ Class Preferred Term	Treatment Group		Total (N = 134) n (%)
	JZP-258 (N = 69) n (%)	Placebo (N = 65) n (%)	
Any TEAE	13 (18.8)	22 (33.8)	35 (26.1)
Infections and Infestations	7 (10.1)	5 (7.7)	12 (9.0)
Nasopharyngitis	2 (2.9)	2 (3.1)	4 (3.0)
Influenza	0	2 (3.1)	2 (1.5)
Urinary Tract Infection	2 (2.9)	0	2 (1.5)
Nervous System Disorders	2 (2.9)	11 (16.9)	13 (9.7)
Cataplexy	1 (1.4)	5 (7.7)	6 (4.5)
Somnolence	0	6 (9.2)	6 (4.5)
Poor Quality Sleep	0	2 (3.1)	2 (1.5)
Psychiatric Disorders	1 (1.4)	7 (10.8)	8 (6.0)
Sleep Disorder	0	3 (4.6)	3 (2.2)
Insomnia	0	2 (3.1)	2 (1.5)
Nightmare	0	2 (3.1)	2 (1.5)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OLE = Open-label Extension; SOC = system organ class; TEAE = treatment-emergent adverse event

Adverse events were coded using MedDRA, version 19.1. Treatment-emergent AEs were defined as any AEs that started or worsened in severity on or after the first dose of double-blind study drug up to 1) the last dose of double-blind study drug + 30 days for subjects who did not enter the OLE, 2) the first dose of study drug during the OLE for subjects who rolled over into the OLE immediately after having completed the Main Study or 3) whichever occurred first between the following 2 timepoints for subjects who rolled over into the OLE after having re-entered into the study: last dose of double-blind study drug + 30 days or first dose of study drug during the OLE. Subjects reporting an AE more than once within an SOC/preferred term were counted only once within that SOC/preferred term. A subject could have had > 1 preferred term under a given SOC.

Percentages were based on the total number of subjects in the analysis population reported in each column.

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As the table indicates, all individual adverse events in the “Nervous System Disorders” and “Psychiatric Disorders” categories were more frequent in the placebo group than in the Xywav group during that period. These include cataplexy, somnolence, poor quality sleep, sleep disorders, and insomnia, nightmares.

8.2.7.1.2 Safety Laboratory Tests

There are no items of special concern in regard to Xywav in the sponsor’s display and analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during this study. These analyses, like other analyses of safety data were based on pre-randomization treatment group across the mainly open-label phases of the main study.

8.2.7.1.3 Vital Signs

The changes observed in blood pressure, pulse rate, respiratory rate, and temperature during this study were unremarkable and did not appear to be of clinical significance. As with other safety analyses, these were based on pre-randomization treatment group across the mainly open-label phases of the main study.

8.2.7.1.4 Body Weight

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

8.2.7.1.5 Electrocardiograms

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

8.2.7.1.6 Columbia-Suicide Severity Rating Scale

Two patients had suicidal ideation based on the Columbia-Suicide Severity Rating Scale during the open-label optimized treatment and titration period. Neither patient had an adverse event recorded as suicidal ideation or behavior during the main study. One of those patients had a prior history of suicidal ideation which was also manifest on Day 1 of the open-label optimized treatment and titration period. The other patient had a prior history of depression, and reported depression during the study as well.

8.2.7.1.7 Pregnancy

A patient, aged 19 years, had a positive pregnancy test on Day 34 of the open-label optimized treatment and titration period. She belonged to the Xyrem® plus other anti-cataplectic pre-randomization group. Study medication was

discontinued when she became aware of the positive pregnancy test. A month later she underwent an induced abortion for non-medical reasons.

8.2.7.2 Open-Label Extension Phase

8.2.7.2.1 All Adverse Events Occurring During Open-Label Extension Period

Adverse events that occurred in > 1 subject in the open-label extension period are summarized in the next sponsor table.

System Organ Class Preferred Term	Re-entry Subjects (N = 27) n (%)	Rollover Subjects (N = 47) n (%)	Total (N = 74) n (%)
Any TEAE	16 (59.3)	27 (57.4)	43 (58.1)
Gastrointestinal disorders	4 (14.8)	4 (8.5)	8 (10.8)
Abdominal pain	0	2 (4.3)	2 (2.7)
Diarrhoea	2 (7.4)	0	2 (2.7)
General disorders and administration site conditions	1 (3.7)	4 (8.5)	5 (6.8)
Fatigue	1 (3.7)	1 (2.1)	2 (2.7)
Infections and infestations	7 (25.9)	15 (31.9)	22 (29.7)
Nasopharyngitis	3 (11.1)	3 (6.4)	6 (8.1)
Influenza	0	4 (8.5)	4 (5.4)
Upper respiratory tract infection	1 (3.7)	3 (6.4)	4 (5.4)
Rhinitis	1 (3.7)	2 (4.3)	3 (4.1)
Urinary tract infection	1 (3.7)	1 (2.1)	2 (2.7)
Nervous system disorders	9 (33.3)	7 (14.9)	16 (21.6)
Headache	4 (14.8)	3 (6.4)	7 (9.5)
Dizziness	3 (11.1)	2 (4.3)	5 (6.8)
Psychiatric disorders	2 (7.4)	3 (6.4)	5 (6.8)
Anxiety	1 (3.7)	2 (4.3)	3 (4.1)
Reproductive system and breast disorders	2 (7.4)	4 (8.5)	6 (8.1)
Dysmenorrhoea	2 (7.4)	1 (2.1)	3 (4.1)

System Organ Class Preferred Term	Re-entry Subjects (N = 27) n (%)	Rollover Subjects (N = 47) n (%)	Total (N = 74) n (%)
Respiratory, thoracic and mediastinal disorders	2 (7.4)	4 (8.5)	6 (8.1)
Nasal congestion	0	2 (4.3)	2 (2.7)
Oropharyngeal pain	1 (3.7)	1 (2.1)	2 (2.7)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OLE = Open-label Extension; SOC = system organ class; TEAE = treatment-emergent adverse event

Adverse events were coded using MedDRA, version 19.1.

Treatment-emergent AEs were defined as any AEs that started or worsened in severity on or after the first dose of open-label study drug during the OLE up to the last dose of study drug + 30 days.

Subjects reporting an AE more than once within a SOC/preferred term were counted only once within that SOC/preferred term. A subject could have had > 1 preferred term under a given SOC.

Percentages were based on the total number of subjects in the analysis population reported in each column (N).

8.2.7.2.2 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

8.2.7.2.2.1 Deaths

No deaths occurred during the open-label extension phase.

8.2.7.2.2.2 Serious Adverse Events

Only a single serious adverse event occurred during the open-label extension phase: a patient developed invasive ductal breast carcinoma. I have read the narrative for that adverse event, a further description of which is not needed.

8.2.7.2.2.3 Discontinuations Due To Adverse Events

Three patients discontinued open-label JZP-258 during the open-label extension phase of this study on account of adverse events. These patients were as follows:

- The patient above who developed invasive ductal breast carcinoma also as a serious adverse event.
- A patient with apathy.
- A patient with sleep apnea syndrome (this patient had a prior history of obstructive sleep apnea).

I have read the narratives for the above events which do not warrant a further description in this review

8.2.7.2.3 Safety Laboratory Tests

As in the main study, there are no items of special concern in regard to Xywav in the sponsor's analysis of the data from standard hematology, clinical chemistry, and urinalysis parameters observed during the open-label extension phase of this study.

8.2.7.2.4 Vital Signs

The observations blood pressure, pulse rate, respiratory rate, and temperature during the open-label extension were also unremarkable and did not yield any items of clinical significance.

8.2.7.2.5 Body Weight

The body weight data for the open-label extension yielded no data of clinical import.

8.2.7.2.6 Electrocardiograms

The electrocardiographic data for the open-label extension were unremarkable.

8.2.7.2.7 Columbia-Suicide Severity Rating Scale

A single subject in the non-Xyrem anti-cataplectic pre-randomization group reported suicidal ideation at entry into the open-label extension study, and past suicidal ideation at entry into the main study. She had no suicidal ideation on the Columbia-Suicide Severity Rating Scale during any part of the study and no relevant adverse events.

8.2.7.2.8 Pregnancy

No patients became pregnant during the open-label extension study.

8.2.7.3 *Adverse Events Of Special Interest Across Study*

Treatment-emergent adverse events of special interest were pre-specified in the study protocol. These were pre-specified based on a number of factors including the known safety profile of sodium oxybate, the pharmacological properties of JZP-258, and other items.

Treatment-emergent adverse events of special interest, occurring during all study periods in patients administered Xywav (but not in patients administered placebo) are summarized in the following table, which I have copied from the submission.

Special Interest Category System Organ Class Preferred Term	Pre-randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticataplectic (N=23) n (%)	Non-Xyrem Anticataplectic (N=36) n (%)	Naive (N=90) n (%)	
Overall	6 (11.5)	7 (30.4)	13 (36.1)	33 (36.7)	59 (29.4)
Anxiety	2 (3.8)	2 (8.7)	2 (5.6)	8 (8.9)	14 (7.0)
Psychiatric Disorders	2 (3.8)	2 (8.7)	2 (5.6)	8 (8.9)	14 (7.0)
Anxiety	0	1 (4.3)	2 (5.6)	6 (6.7)	9 (4.5)
Tension	1 (1.9)	1 (4.3)	0	0	2 (1.0)
Agitation	1 (1.9)	0	0	0	1 (0.5)
Panic Attack	0	0	0	1 (1.1)	1 (0.5)
Stress	0	0	0	1 (1.1)	1 (0.5)
Confusion	0	1 (4.3)	1 (2.8)	1 (1.1)	3 (1.5)
Psychiatric Disorders	0	1 (4.3)	1 (2.8)	1 (1.1)	3 (1.5)
Confusional State	0	1 (4.3)	0	1 (1.1)	2 (1.0)

Special Interest Category System Organ Class Preferred Term	Pre-randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticatataplectic (N=23) n (%)	Non-Xyrem Anticatataplectic (N=36) n (%)	Naive (N=90) n (%)	
Disorientation	0	0	1 (2.8)	0	1 (0.5)
Depressed Consciousness	2 (3.8)	1 (4.3)	0	2 (2.2)	5 (2.5)
Nervous System Disorders	2 (3.8)	1 (4.3)	0	2 (2.2)	5 (2.5)
Somnolence	2 (3.8)	1 (4.3)	0	2 (2.2)	5 (2.5)
Depression and Suicidality	1 (1.9)	1 (4.3)	4 (11.1)	6 (6.7)	12 (6.0)
Psychiatric Disorders	1 (1.9)	1 (4.3)	4 (11.1)	6 (6.7)	12 (6.0)
Depressed Mood	0	1 (4.3)	3 (8.3)	3 (3.3)	7 (3.5)
Depression	1 (1.9)	0	1 (2.8)	3 (3.3)	5 (2.5)
Psychotic and Dissociative Disorders	0	2 (8.7)	1 (2.8)	0	3 (1.5)
Psychiatric Disorders	0	2 (8.7)	1 (2.8)	0	3 (1.5)
Aggression	0	1 (4.3)	0	0	1 (0.5)
Depersonalisation/derealisation Disorder	0	0	1 (2.8)	0	1 (0.5)
Hallucination, Visual	0	1 (4.3)	0	0	1 (0.5)
Impaired Attention or Cognition	1 (1.9)	0	0	3 (3.3)	4 (2.0)
Nervous System Disorders	1 (1.9)	0	0	3 (3.3)	4 (2.0)
Cognitive Disorder	1 (1.9)	0	0	1 (1.1)	2 (1.0)
Disturbance in Attention	0	0	0	1 (1.1)	1 (0.5)
Memory Impairment	0	0	0	1 (1.1)	1 (0.5)
Parasomnias	1 (1.9)	1 (4.3)	5 (13.9)	8 (8.9)	15 (7.5)
Nervous System Disorders	0	0	1 (2.8)	1 (1.1)	2 (1.0)
Sleep paralysis	0	0	1 (2.8)	1 (1.1)	2 (1.0)
Psychiatric Disorders	1 (1.9)	1 (4.3)	4 (11.1)	7 (7.8)	13 (6.5)
Somnambulism	1 (1.9)	0	1 (2.8)	2 (2.2)	4 (2.0)
Abnormal Dreams	0	0	0	2 (2.2)	2 (1.0)
Sleep Inertia	0	0	1 (2.8)	1 (1.1)	2 (1.0)
Sleep-related Eating Disorder	0	1 (4.3)	0	1 (1.1)	2 (1.0)
Abnormal Sleep-related Event	0	0	1 (2.8)	0	1 (0.5)
Nightmare	0	0	1 (2.8)	0	1 (0.5)
Rapid Eye Movements Sleep Abnormal	0	0	0	1 (1.1)	1 (0.5)
Sleep Talking	0	0	1 (2.8)	0	1 (0.5)
Sleep Terror	0	0	1 (2.8)	0	1 (0.5)
Respiratory Failure and Respiratory Depression	0	0	1 (2.8)	0	1 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	0	0	1 (2.8)	0	1 (0.5)
Sleep Apnoea Syndrome	0	0	1 (2.8)	0	1 (0.5)
Substance Related Disorders	2 (3.8)	3 (13.0)	8 (22.2)	15 (16.7)	28 (13.9)
General Disorders and Administration Site Conditions	1 (1.9)	1 (4.3)	1 (2.8)	2 (2.2)	5 (2.5)

Special Interest Category System Organ Class Preferred Term	Pre-randomization Group				Total (N=201) n (%)
	Xyrem Only (N=52) n (%)	Xyrem + Other Anticatataplectic (N=23) n (%)	Non-Xyrem Anticatataplectic (N=36) n (%)	Naive (N=90) n (%)	
Feeling Drunk	1 (1.9)	0	1 (2.8)	1 (1.1)	3 (1.5)
Drug Withdrawal Syndrome	0	1 (4.3)	0	1 (1.1)	2 (1.0)
Injury, Poisoning and Procedural Complications	0	1 (4.3)	0	0	1 (0.5)
Accidental Overdose	0	1 (4.3)	0	0	1 (0.5)
Nervous System Disorders	2 (3.8)	1 (4.3)	7 (19.4)	13 (14.4)	23 (11.4)
Dizziness	2 (3.8)	1 (4.3)	7 (19.4)	13 (14.4)	23 (11.4)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OLE = Open-label Extension; OL OTTP = Open-label Optimized Treatment and Titration Period; SOC = system organ class;

TEAE = treatment-emergent adverse event

Data collected while subjects randomized to placebo were on placebo during the Double-blind Randomized-withdrawal Period plus the minimum of up to 30 days after completion of the Double-blind Randomized-withdrawal Period or the start of the OLE are excluded from this summary.

Adverse events were coded using MedDRA, version 19.1.

Treatment-emergent AEs were defined as any AEs that started or worsened in severity on or after the first dose of open-label study drug up to the last dose of study drug during the OL OTTP, Stable Dose Period, Double-blind Randomized-withdrawal Period or OLE period (whichever was the latest) + 30 days, excluding AEs that started or worsened in severity after the last dose of study drug during the Double-blind Randomized-withdrawal Period + 30 days, but before the first dose of the OLE period for subjects re-entering into the study.

Subjects reporting an AE more than once within an SOC/preferred term were counted only once within that SOC/preferred term. A subject could have had > 1 preferred term under a given SOC.

Percentages were based on the total number of subjects in the analysis population reported in each column (N).

8.2.7.4 Potential Abuse And Misuse Of JZP-258 Across Study

The sponsor has summarized data pertaining to abuse and misuse across the study. I have reviewed those data from which it appears that only a single patient may have abused or misused study drug over the course of the study. This patient returned fewer empty bottles of study medication than expected, with no clear explanation forthcoming. This patient later discontinued study medication, during the main study, on account of a depressed mood.

8.3 Sponsor's Conclusions

The sponsor's salient conclusions based on the results of this study were as follows.

- JZP-258 had efficacy in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. These results were robust and consistent across sensitivity and subgroup analyses.
- JZP-258 was well-tolerated by adults with narcolepsy. The safety profile of JZP-258 in this study was consistent with that of oxybate.

8.4 Reviewer's Summary Comments

8.4.1 Study Design

Protocol 15-006 had the following core features.

- The primary objective of the study was to evaluate the efficacy of JZP-258 in the treatment of cataplexy in patients with narcolepsy. A key secondary objective was to evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness in patients with narcolepsy.
- This was a double-blind, placebo-controlled, randomized withdrawal multicenter study of the efficacy and safety of JZP-258. Patients enrolled in the study included those whose prior treatment status is in any of the following categories:
 1. Treatment with a stable dose of Xyrem alone for at least 2 months prior to screening.
 2. Treatment with a stable dose of Xyrem and an unapproved anti-cataplectic for at least 2 months prior to screening.
 3. Treatment with an unapproved anti-cataplectic, but no treatment with Xyrem.
 4. No prior treatment with Xyrem or an unapproved anti-cataplectic.
- The study consisted of the following consecutive periods: screening; open-label titration and treatment optimization (of variable duration up to a maximum of 12 weeks, depending on prior treatment status); open-label stable-dose treatment (2 weeks); double-blind randomized withdrawal (2 weeks); and safety follow-up (2 weeks). All study patients (i.e., patients in all 4 entry categories) were to be titrated (during the variable-duration open-label titration period) to a dose of JZP-258 that was deemed both effective and tolerable and was maintained for at least 2 weeks prior to entering the two-week open-label stable-dose period.
- A total of about 185 patients were planned to be enrolled in the study of whom about 130 patients were expected to enter the double-blind withdrawal period during which they were to be randomly assigned 1:1 to either continuing the same dose of JZP-258 taken during the stable dose period or to placebo.
- The main inclusion criteria for this study were as follows: men and women, aged 18 to 70 years; a primary diagnosis of narcolepsy with cataplexy that met the ICSD-3 criteria or DSM-5 criteria; a history of having at least 14 cataplexy attacks in a typical two-week period and clinically significant symptoms of excessive daytime sleepiness prior to any narcolepsy treatment; treatment status prior to study entry consisting of one of the aforementioned 4 categories; if currently treated with Xyrem, must have had documented improvement documented clinical improvement of cataplexy and excessive daytime sleepiness; and if treated with a

stimulant for narcolepsy, must have been at an unchanged dose for at least 2 months prior to dosing or must not have been treated at all with a stimulant.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks from the 2-week stable dose period to the 2-week double-blind treatment period. The key secondary efficacy parameter was the change in in Epworth Sleepiness Scale score from the 2-week stable dose period to the 2-week double-blind treatment period. A number of other efficacy endpoints were also under evaluation in this study including the Patient Global Impression of Change for narcolepsy overall; the Clinical Global Impression of Change for narcolepsy overall; the change in quality of life based on the Short Form-36 score, and EuroQol 5 Dimensions Self-Report Questionnaire. Safety measures were to include adverse events, vital signs, weight, physical examinations, 12-lead electrocardiograms, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and the Columbia-Suicide Severity Rating Scale (for assessing suicidality).
- The final analysis of the primary efficacy parameter and key secondary efficacy parameters was to employ a fixed sequential testing strategy in which the initial step will involve a comparison of JZP-258 with placebo for the primary efficacy parameter; if the initial comparison was statistically significant (currently $p \leq 0.05$), the treatment groups would then be compared on the key secondary efficacy parameter at the same level of statistical significance (currently $p \leq 0.05$). An analysis of covariance model was to be used at both steps.
- The main study was to be followed by an open-label extension study (phase) lasting 24 weeks. Patients could enter the open-label phase of the study in two categories, as further described immediately below: rollover subjects, comprising those who entered the open-label extension study directly from the main study, with Visit 16 being both the last day of the main study and first day of the open-label extension study; and re-entry subjects, comprising those entered the open-label extension study directly after completion of the main study.

8.4.2 Study Results

Study 15-006 was conducted in a manner consistent with the study protocol.

201 patients were enrolled in the study. They consisted of: 52 patients who were receiving Xyrem only; 23 patients were receiving a combination of Xyrem® and another (unapproved) anti-cataplectic drug; 36 patients were on a non-Xyrem (unapproved) anti-cataplectic drug; and 90 patients were drug-naïve at study entry. All 201 patients entered the main study in the optimized treatment and titration period (12 weeks). 155 patients completed that period, of whom 149

patients entered the stable-dose period (2 weeks). 144 out of 149 patients completed the stable-dose period.

136 out of 144 patients who completed the stable-dose period were then randomized, entering the randomized, double-blind, placebo-controlled, withdrawal period (2 weeks). At the beginning of that period, 69 patients were randomized to JZP-258 and 67 patients were randomized to placebo; all 69 patients randomized to JZP-258 and all 59 patients randomized to placebo completed the study.

The primary efficacy analysis (based on an analysis of covariance) indicated that the mean change from baseline over the two-week randomized withdrawal period in the weekly number of cataplexy attacks was 11.46 for the placebo group and 0.12 for the group that continued to take JZP-258 (this change was an increase in cataplexy frequency). This difference was statistically significant ($p < 0.0001$). Statistically significant treatment differences favoring JZP-258 over placebo were seen on the key secondary efficacy parameter analyzed in the prespecified sequence: the change from baseline in modified Epworth Sleepiness Scale score was 3.0 in the placebo group and 0.0 in the group that continued to take JZP-258 ($p < 0.0001$).

74 patients then entered the open-label extension study; 67 patients completed that part of the study.

The adverse event profile of Xywav as seen in this study was not substantially different from that seen with Xyrem. The other safety outcomes did not reveal any concern.

9. 120-Day Safety Update

The description of data from the 120-Day Safety Update has been incorporated into the previous section.

10. Additional Clinical Studies Of JZP-258

10.1 Overall Summary

As already noted, three further clinical studies of JZP-258 have been submitted in support of this application. These studies are as follows

- Two clinical pharmacology studies: 13-010 and JZP258-101.
- A clinical study evaluating the taste of JZP-258: 15-003.

Each of these additional studies is further summarized in the table below that I have extracted from a table in this submission.

Note that all the studies listed in the table below were conducted in healthy subjects.

Study Identifier; Status; Report Type	Type of Study	Study Design and Type of Control	Primary Objective(s) of the Study	Product, Route, Dose and Duration of Treatment	Subject Population; Age (mean [range]: years)
13-010 Completed Full CSR	PK and BA / BE	Phase 1 open-label, randomized crossover study	To assess the relative BA and BE of JZP-258 compared with Xyrem under fasting and fed conditions To evaluate the PK of JZP-258 under fasting and fed conditions (food effect) To evaluate the relative BA and BE of 2 admixtures of JZP-258 and Xyrem at different ratios compared with Xyrem oral solution under fasting conditions To evaluate the PK of JZP-258 2.25 g under fasting conditions	JZP-258 and / or Xyrem; oral; <i>Part 1:</i> • Treatment A: 4.5 g JZP-258, diluted with 51 mL water, under fasting conditions, taken with 180 mL water • Treatment B: 4.5 g JZP-258, diluted with 51 mL water, under fed conditions, taken with 180 mL water • Treatment C: 4.5 g Xyrem, diluted with 51 mL of water, under fasting conditions, taken with 180 mL water • Treatment D: 4.5 g Xyrem, diluted with 51 mL of water, under fed conditions, taken with 180 mL water <i>Part:</i> • Treatment E: Admixture of 2.5 g JZP-258 and 2 g Xyrem, (total of 4.5 g oxybate) diluted with 51 mL water, taken with 180 mL water, under fasting conditions • Treatment F: Admixture of 3.75 g JZP-258 and 0.75 g Xyrem (total of 4.5 g oxybate) diluted with 51 mL water, taken with 180 mL water, under fasting conditions • Treatment G: 4.5 g Xyrem diluted with 51 mL water, taken with 180 mL water, under fasting conditions • Treatment H: 2.25 g JZP-258 diluted with	<i>Part 1:</i> 36 healthy volunteers Age: 27.6 years Range: 22 to 43 years <i>Part 2:</i> 24 healthy volunteers Age: 26.7 years Range: 20 to 46 years
				51 mL of water, taken with 180 mL water, under fasting conditions All treatments were administered as single doses. Duration of treatment: up to 9 days	
JZP258-101 Complete Full CSR	PK and BA / BE	Phase 1 open-label, randomized crossover study	To assess the relative BA and BE of JZP-258 oral solution versus Xyrem taken with 60 mL water under fasting conditions	JZP-258 and Xyrem; oral; • Treatment A: 4.5 g JZP-258 taken with 60 mL water under fasting conditions • Treatment B: 4.5 g Xyrem taken with 60 mL water under fasting conditions • Treatment C: 4.5 g JZP-258 taken with 60 mL water under fed conditions • Treatment D: 4.5 g Xyrem taken with 60 mL water under fed conditions • Treatment E: 4.5 g Xyrem taken with 240 mL water under fasting conditions • Treatment F: 4.5 g JZP-258 taken with 240 mL water under fasting conditions All treatments were administered as single doses. Duration of treatment: up to 12 days	48 healthy volunteers Age: 25.4 years Range: 19 to 44 years

Study Identifier; Status; Report Type	Type of Study	Study Design and Type of Control	Primary Objective(s) of the Study	Product, Route, Dose and Duration of Treatment	Subject Population; Age (mean [range]: years)
15-003 Completed Full CSR	Taste Testing Study	Phase 1 randomized, double-blind, crossover taste testing study	The primary objective was to compare the taste of JZP-258 to placebo (both diluted with water) for sameness.	JZP-258 or placebo; oral taste A 4-sequence, 4-period, 2-treatment, replicate crossover design was used to compare Treatment A and Treatment B: - Treatment A: 9 mL (4.5 g) of JZP-258 oral solution (500 mg/mL), diluted with 60 mL water - Treatment B: 9 mL of placebo solution (aqueous solution containing 389 mg/mL sodium citrate, 1.3 mg/mL malic acid, and 1.2 mg/mL sucralose), diluted with 60 mL water Duration of treatment: up to 3 days	68 healthy volunteers Age: 24.5 years Range: 18 to 50 years

Abbreviations: BA = bioavailability; BE = bioequivalence; PK = pharmacokinetics.

Note that neither JZP-258 nor placebo was intended to be swallowed in Study 15-003.

10.2 Safety Results

10.2.1 Study 13-010

10.2.1.1 Treatment -Emergent Adverse Events

10.2.1.1.1 Overview Of Adverse Events

The following sponsor tables provides an overview of all treatment-emergent adverse events that occurred in both parts of this study. The table is self-explanatory.

Category	Number of subjects, n (%)				
Part 1	Treatment A N = 35	Treatment B N = 36	Treatment C N = 36	Treatment D N = 36	Overall N = 36
Subjects with at least 1 TEAE	34 (97.1)	33 (91.7)	36 (100)	33 (91.7)	36 (100)
Subjects with related TEAEs	34 (97.1)	32 (88.9)	36 (100)	32 (88.9)	36 (100)
Subjects who discontinued due to a TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any severe TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Part 2	Treatment E N = 23	Treatment F N = 22	Treatment G N = 23	Treatment H N = 23	Overall N = 24
Subjects with at least 1 TEAE	23 (100)	22 (100)	23 (100)	18 (78.3)	24 (100)
Subjects with related TEAEs	23 (100)	22 (100)	23 (100)	17 (73.9)	24 (100)
Subjects who discontinued due to a TEAE	2 (8.7)	0 (0.0)	2 (8.7)	0 (0.0)	3 (12.5)
Any severe TEAEs	5 (21.7)	2 (9.1)	2 (8.7)	0 (0.0)	7 (29.2)
Subjects with serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: TEAE = treatment-emergent adverse event.

Treatment A: 4.5 g JZP-258, diluted with 51 mL water, under fasting conditions, taken with 180 mL water.

Treatment B: 4.5 g JZP-258, diluted with 51 mL water, under fed conditions, taken with 180 mL water.

Treatment C: 4.5 g Xyrem, diluted with 51 mL water, under fasting conditions, taken with 180 mL water.

Treatment D: 4.5 g Xyrem, diluted with 51 mL water, under fed conditions, taken with 180 mL water.

Treatment E: Admixture of JZP-258 2.5 g and 2 g Xyrem (total 4.5 g oxybate) diluted with 51 mL water, taken with 180 mL water, under fasting conditions.

Treatment F: Admixture of JZP-258 3.75 g and 0.75 g Xyrem (total 4.5 g oxybate) diluted with 51 mL water, taken with 180 mL water, under fasting conditions.

Treatment G: 4.5 g Xyrem diluted with 51 mL water, taken with 180 mL water, under fasting conditions.

Treatment H: 2.25 g JZP-258 diluted with 51 mL water, taken with 180 mL water, under fasting conditions.

Notes: The denominator for percentages overall is based on the number of subjects in the Safety Population.

10.2.1.1.2 Common Adverse Events

All subjects enrolled in both Parts 1 and Part 2 experienced treatment-emergent adverse events as the preceding table notes. Most treatment-emergent adverse events were judged to be mild.

The most common treatment-emergent adverse events in Part 1, regardless of treatment group, were somnolence (97.2%), dizziness (83.3%), nausea (55.6%), headache (36.1%), and fatigue (27.8%). The most common treatment-emergent adverse events in Part 2, regardless of dose were somnolence (100.0%), dizziness (91.7%), nausea (58.3%), vomiting (37.5%), and headache (33.3%). The incidence percentages in each instance refers to all treatment groups combined.

10.2.1.1.3 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

There were no deaths or serious adverse events in this study.

Three subjects discontinued from the study on account of adverse events. All 3 subjects experienced vomiting after receiving study medication: 1 subject had received JZP-258 2.5 g combined with Xyrem 2 g when fasted, and 2 subjects had received Xyrem 4.5 g when fasted.

10.2.1.2 Clinical Laboratory Evaluations

No clinically significant abnormalities were observed.

10.2.1.3 Vital Signs And Other Observations Related To Safety

No clinically noteworthy changes in vital signs or other safety parameters were noted except for 6 subjects who developed blood oxygen saturation levels less than 95% after various doses of study medication (the lowest was 90%). A further subject had a single blood oxygen saturation measurement of 71%, after receiving Xyrem in the fasted state. All abnormalities of oxygen saturation resolved by the end of the study.

10.2.2 Study JZP258-101

10.2.2.1 Treatment -Emergent Adverse Events

10.2.2.1.1 Overview Of Adverse Events

The following sponsor tables provides an overview of all treatment-emergent adverse events that occurred during this study. The table is self-explanatory. As the table indicates, all patients enrolled in this study had at least one treatment-emergent adverse event.

Category	Number of subjects, n (%)						Overall N = 48
	Treatment A N = 47	Treatment B N = 47	Treatment C N = 46	Treatment D N = 46	Treatment E N = 47	Treatment F N = 47	
Subjects with at least 1 TEAE	44 (93.6)	46 (97.9)	40 (87.0)	41 (89.1)	45 (95.7)	45 (95.7)	48 (100)
Subjects with related TEAEs	44 (93.6)	46 (97.9)	40 (87.0)	41 (89.1)	45 (95.7)	44 (93.6)	48 (100)
Subjects who discontinued due to a TEAE	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	3 (6.3)
Any severe TEAEs	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.2)
Subjects with serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE = treatment-emergent adverse event.

Treatment A: 4.5 g JZP-258 taken with 60 mL water under fasting conditions.

Treatment B: 4.5 g Xyrem taken with 60 mL water under fasting conditions.

Treatment C: 4.5 g JZP-258 taken with 60 mL water under fed conditions.

Treatment D: 4.5 g Xyrem taken with 60 mL water under fed conditions.

Treatment E: 4.5 g Xyrem taken with 240 mL water under fasting conditions.

Treatment F: 4.5 g JZP-258 taken with 240 mL water under fasting conditions.

10.2.2.1.2 Common Adverse Events

A summary of treatment-emergent adverse events that occurred in $\geq 5\%$ of subjects during any treatment period is in the following table, which is self-explanatory.

Preferred Term	Number (%) of Subjects					
	Trt A JZP-258 N=47	Trt B Xyrem N=47	Trt C JZP-258 N=46	Trt D Xyrem N=46	Trt E Xyrem N=47	Trt F JZP-258 N=47
	60 mL Water, Fasting		60 mL Water, Fed		240 mL Water, Fasting	
Somnolence	39 (83.0)	41 (87.2)	34 (73.9)	33 (71.7)	38 (80.9)	37 (78.7)
Dizziness	22 (46.8)	23 (48.9)	21 (45.7)	18 (39.1)	24 (51.1)	19 (40.4)
Nausea	13 (27.7)	21 (44.7)	5 (10.9)	3 (6.5)	16 (34.0)	16 (34.0)
Headache	9 (19.1)	10 (21.3)	7 (15.2)	10 (21.7)	6 (12.8)	10 (21.3)
Fatigue	5 (10.6)	5 (10.6)	4 (8.7)	3 (6.5)	1 (2.1)	2 (4.3)
Paraesthesia	5 (10.6)	11 (23.4)	6 (13.0)	5 (10.9)	5 (10.6)	3 (6.4)
Vertigo	4 (8.5)	8 (17.0)	2 (4.3)	3 (6.5)	6 (12.8)	5 (10.6)
Euphoric mood	6 (12.8)	2 (4.3)	3 (6.5)	2 (4.3)	1 (2.1)	1 (2.1)
Abdominal pain	3 (6.4)	5 (10.6)	2 (4.3)	0	1 (2.1)	2 (4.3)
Muscle twitching	1 (2.1)	3 (6.4)	0	1 (2.2)	3 (6.4)	3 (6.4)
Feeling drunk	4 (8.5)	4 (8.5)	2 (4.3)	1 (2.2)	3 (6.4)	4 (8.5)
Vision blurred	3 (6.4)	5 (10.6)	0	0	3 (6.4)	3 (6.4)
Feeling hot	2 (4.3)	2 (4.3)	1 (2.2)	1 (2.2)	3 (6.4)	1 (2.1)
Vomiting	2 (4.3)	3 (6.4)	0	1 (2.2)	3 (6.4)	1 (2.1)
Back pain	0	1 (2.1)	0	1 (2.2)	3 (6.4)	3 (6.4)
Abdominal discomfort	1 (2.1)	0	4 (8.7)	1 (2.2)	1 (2.1)	0
Muscular weakness	0	3 (6.4)	2 (4.3)	0	1 (2.1)	0
Limb discomfort	2 (4.3)	3 (6.4)	1 (2.2)	1 (2.2)	1 (2.1)	2 (4.3)
Thirst	0	0	1 (2.2)	1 (2.2)	4 (8.5)	2 (4.3)
Disturbance in attention	2 (4.3)	3 (6.4)	1 (2.2)	1 (2.2)	1 (2.1)	0
Depression	0	0	0	1 (2.2)	3 (6.4)	3 (6.4)
Myalgia	0	3 (6.4)	0	2 (4.3)	1 (2.1)	0
Asthenia	0	3 (6.4)	0	0	1 (2.1)	0
Paraesthesia oral	0	2 (4.3)	1 (2.2)	0	3 (6.4)	1 (2.1)
Visual impairment	0	3 (6.4)	0	1 (2.2)	0	0

Note: Table includes preferred terms with incidence of $\geq 5\%$ during any treatment (Trt). The denominators for percentages by treatment were based on the number of subjects exposed to that treatment in the Safety Population. MedDRA (Version 19.0) was used for coding.

10.2.2.1.3 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

There were no deaths or serious adverse events during this study.

3 subjects discontinued study medication on account of adverse events: 1 subject had an intermittent bradypnea, 1 subject had folliculitis, and 1 subject had a second-degree atrioventricular block (Wenckebach type). All subjects received Xyrem 4.5 g under fasted conditions.

10.2.2.2 Clinical Laboratory Evaluations

No clinically significant laboratory abnormalities were seen during this study.

10.2.2.3 Vital Signs And Other Observations Related To Safety

No clinically significant changes in heart rate or blood pressure were noted during the study.

A single subject (who did not discontinue study medication) had respiratory rate recordings of 6 breaths/minute after receiving Xyrem® in a fasted stated. No study subject experienced oxygen desaturation during the study.

With the exception of the subject who had a second-degree atrioventricular block (Wenckebach type), no clinically significant electrocardiographic abnormalities appear to have been observed.

10.2.3 Study 15-003

Note again, that neither JZP-258 nor placebo was intended to be swallowed during this study.

10.2.3.1 Treatment -Emergent Adverse Events

10.2.3.1.1 Overview Of Adverse Events

The following sponsor tables provides an overview of all treatment-emergent adverse events that occurred during this study. The table is self-explanatory. As the table indicates, 11.8% of patients enrolled in this study had at least one treatment-emergent adverse event.

10.2.3.1.2 Common Adverse Events

All treatment-emergent adverse events that occurred during this study are summarized in the following table, which I have copied from the submission.

Adverse Events by Preferred Term ^a	Number of subjects, n (%)
	Overall N = 68
Subjects with at least 1 TEAE	8 (11.8)
Headache	2 (2.9)
Migraine	1 (1.5)
Somnolence	1 (1.5)
Myalgia	2 (2.9)
Nausea	1 (1.5)
Fatigue	1 (1.5)
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.	
^a AEs were coded using MedDRA Version 19.1.	

10.2.3.1.3 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

There were no deaths, serious adverse events, or discontinuations due to adverse events during this study.

10.2.3.2 Clinical Laboratory Evaluations

In this study, clinical laboratory evaluations were conducted at screening only.

10.2.3.3 Vital Signs And Other Observations Related To Safety

No clinically significant changes in vital signs or other safety parameters were observed during this study.

10.3 Summary Pharmacokinetic Results And Conclusions

The following presentation of study results and conclusions is entirely based on data provided by the sponsor. For additional analyses, please see the clinical pharmacology review of this submission

10.3.1 Study 13-010

10.3.1.1 Key Results

10.3.1.1.1 Part 1

The following two sponsor tables summarize the pharmacokinetic results of Part 1 of this study.

Part 1: Oxybate Plasma Pharmacokinetic Parameters Following a Single Dose of JZP-258 or Xyrem Under Fasted and Fed Conditions (PK Completer Population, N=30)

Treatment	Mean (CV%)				
	C_{max} (µg/mL)	T_{max}^a (h)	$t_{1/2}$ (h)	AUC_{0-t} (µg·h/mL)	AUC_{0-inf} (µg·h/mL)
JZP-258 Fasted	101.8 (21.2)	0.75 (0.33-1.50)	0.57 (21.9)	235.4 (32.3)	236.5 (32.3)
JZP-258 Fed	77.4 (25.0)	0.75 (0.33-2.50)	0.62 (27.0)	213.3 (33.9)	214.8 (34.0)
Xyrem Fasted	135.7 (14.8)	0.50 (0.33-1.00)	0.57 (28.0)	263.9 (30.0)	265.2 (30.1)
Xyrem Fed	84.3 (31.3)	0.75 (0.33-2.50)	0.57 (20.2)	228.0 (33.5)	229.6 (33.5)

a Median (min-max)

Part 1: Statistical Analysis of Oxybate Pharmacokinetic Data Following a Single Dose of JZP-258 or Xyrem Under Fasted and Fed Conditions (PK Completer Population, N=30)

Treatment Comparison	Parameter	% Ratio of Geometric Means	90% CI
JZP-258 Fasted vs Xyrem Fasted	C_{max}	74.21	67.803, 81.222
	AUC_{0-t}	88.29	84.343, 92.423
	AUC_{0-inf}	88.31	84.389, 92.415
JZP-258 Fed vs Xyrem Fed	C_{max}	93.52	85.444, 102.355
	AUC_{0-t}	94.23	90.019, 98.643
	AUC_{0-inf}	94.21	90.029, 98.592
JZP-258 Fed vs JZP-258 Fasted	C_{max}	74.75	68.272, 81.843
	AUC_{0-t}	89.62	85.597, 93.831
	AUC_{0-inf}	89.79	85.786, 93.979
Xyrem Fed vs Xyrem Fasted	C_{max}	59.32	54.176, 64.945
	AUC_{0-t}	83.97	80.200, 87.914
	AUC_{0-inf}	84.16	80.411, 88.091

10.3.1.1.2 Part 2

The following two sponsor tables summarize the pharmacokinetic results of Part 2 of this study.

Part 2. Oxybate Plasma Pharmacokinetic Parameters Following a Single Dose by Treatment (Admixtures of JZP-258 with Xyrem, Xyrem 4.5 g, and JZP-258 2.25 g) Under Fasted Conditions (PK Completer Population, N=16)

Treatment	Mean (CV%)				
	C _{max} (µg/mL)	T _{max} ^a (h)	t _{1/2} (h)	AUC _{0-t} (µg·h/mL)	AUC _{0-inf} (µg·h/mL)
JZP-258 2.5 g & Xyrem 2 g Fasted	112.3 (22.2)	0.64 (0.33-0.75)	0.73 (61.2)	240.0 (39.6)	241.4 (39.5)
JZP-258 3.75 g & Xyrem 0.75 g Fasted	97.0 (17.0)	0.75 (0.33-2.00)	0.95 (65.8)	223.4 (33.4)	225.3 (33.6)
Xyrem 4.5 g Fasted	130.9 (16.5)	0.50 (0.330-0.750)	0.73 (28.2)	246.6 (36.3)	248.2 (36.3)
JZP-258 2.25 g Fasted	51.3 (40.1)	0.75 (0.33-3.00)	0.55 ^b (31.5)	77.7 (49.4)	81.0 (47.5)

a Median (min-max)

b n = 15 for this parameter in this treatment group

Part 2: Statistical Analysis of Oxybate Pharmacokinetic Data Following a Single Dose of Admixtures of JZP-258 with Xyrem, Xyrem 4.5 g, and JZP-258 2.25 g (PK Completer Population, N=16)

Treatment Comparison	Parameter	% Ratio of Geometric Means	90% CI
JZP-258 2.5/Xyrem 2 g Fasted vs Xyrem 4.5 g Fasted	C _{max}	84.82	73.795, 97.489
	AUC _{0-t}	96.46	90.009, 103.376
	AUC _{0-inf}	96.43	90.728, 102.498
JZP-258 3.75/Xyrem 0.75 g Fasted vs Xyrem 4.5 g Fasted	C _{max}	74.13	64.495, 85.203
	AUC _{0-t}	91.22	85.119, 97.761
	AUC _{0-inf}	91.37	85.961, 97.113

10.3.1.2 Conclusions

The sponsor's main conclusions for each part of this study were as follows.

10.3.1.2.1.1 Part 1

- The Agency's bioequivalence criteria were met for plasma oxybate AUC, but not for plasma oxybate C_{max} under fasted conditions. Under fed conditions, bioequivalence criteria were met for plasma oxybate for both C_{max} and AUC.
- Median oxybate T_{max} was slightly delayed for JZP-258 compared with Xyrem under fasted conditions.
- Mean t_{1/2} values were similar for both JZP-258 and Xyrem.

- The presence of food reduced oxybate exposure (C_{max} and AUC) under both fasted and fed conditions, although the results were less pronounced for JZP-258 compared with Xyrem.

10.3.1.2.1.2 Part 2

- For the comparison of each of the 4.5 g admixtures with Xyrem under fasted conditions, the Agency's bioequivalence criteria were met for plasma oxybate AUC but not for plasma oxybate C_{max} .
- Median oxybate T_{max} values were slightly delayed for the admixture treatments compared with Xyrem®.

10.3.2 Study JZP258-101

10.3.2.1 Key Results

The following 3 tables summarized the salient pharmacokinetic results of this study. Additional results are in the full study report.

Oxybate Plasma Pharmacokinetic Parameters (PK Completer Population, N=42)

Treatment	Mean (Coefficient of Variation%)				
	C_{max} ($\mu\text{g/mL}$)	T_{max} ^a (h)	$t_{1/2}$ (h)	AUC_{0-t} ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{0-inf} ($\mu\text{g}\cdot\text{h/mL}$)
Treatment A: JZP-258 60 mL water, fasting	94.63 (20.5)	1.000 (0.33-3.00)	0.6611 (27.5)	241.5 (38.8)	243.1 (39.0)
Treatment B: Xyrem 60 mL water, fasting	123.0 (21.5)	0.520 (0.33-1.52)	0.6503 (26.9)	254.7 (36.4)	256.3 (36.5)
Treatment C: JZP-258 60 mL water, fed	64.80 (27.4)	1.000 (0.33-2.50)	0.7737 (61.3)	206.4 (43.1)	208.6 (43.3)
Treatment D: Xyrem 60 mL water, fed	69.65 (26.4)	0.875 (0.33-3.00)	0.6387 (24.6)	208.2 (41.3)	209.8 (41.5)
Treatment E: Xyrem 240 mL water, fasting	130.5 (20.3)	0.500 (0.33-1.50)	0.6650 (29.5)	262.1 (38.5)	263.6 (38.6)
Treatment F: JZP-258 240 mL water, fasting	96.34 (20.3)	0.750 (0.50-2.50)	0.6835 (36.3)	238.8 (39.8)	240.5 (39.9)

^a Median (minimum-maximum)

Statistical Analysis of Bioequivalence for Oxybate Plasma PK Parameters (PK Completer Population, N=42)

PK Parameter	Geometric LS Means		Test/Reference Ratio (%)	90% CI for Ratio (%)	
	Test	Reference		Lower	Upper
Test Treatment A = JZP-258, Fasting versus Reference Treatment B = Xyrem, Fasting					
AUC _{0-inf} (µg·h/mL)	222.6	236.1	94.27	90.49	98.20
AUC _{0-t} (µg·h/mL)	221.2	234.7	94.24	90.42	98.22
C _{max} (µg/mL)	92.58	120.2	77.05	71.89	82.58

Note: The primary bioequivalence assessment was done on treatments administered with 60 mL water.
Abbreviations: CI = confidence interval; LS = least squares; PK = pharmacokinetic

Statistical Analysis of Oxybate Plasma PK Parameters to Assess Effect of Food (PK Completer Population, N=42)

PK Parameter	Geometric LS Means		Test/Reference Ratio (%)	90% CI for Ratio (%)	
	Test	Reference		Lower	Upper
Test Treatment C = JZP-258, Fed versus Reference Treatment A = JZP-258, Fasting					
AUC _{0-inf} (µg·h/mL)	187.7	222.6	84.34	80.96	87.85
AUC _{0-t} (µg·h/mL)	185.8	221.2	84.00	80.59	87.55
C _{max} (µg/mL)	62.31	92.58	67.30	62.79	72.14
Test Treatment D = Xyrem, Fed versus Reference Treatment B = Xyrem, Fasting					
AUC _{0-inf} (µg·h/mL)	190.6	236.1	80.72	77.49	84.09
AUC _{0-t} (µg·h/mL)	189.1	234.7	80.57	77.30	83.98
C _{max} (µg/mL)	66.88	120.2	55.66	51.93	59.66

Note: The food effect assessments were done on treatments administered with 60 mL water.
Abbreviations: CI = confidence interval; LS = least squares; PK = pharmacokinetic

10.3.2.2 Conclusions

The sponsor's main conclusions for this study were as follows:

- JZP-258 did not meet the Agency's bioequivalence criteria when compared with Xyrem on account of a lower plasma oxybate C_{max} relative to Xyrem.
- JZP-258 had a longer T_{max} than Xyrem.
- For both drugs, food reduced the rate and extent of absorption compared with the fasted state.

10.4 Other Results

Study 15-003 was conducted to evaluate the suitability of the placebo that was used in Study 15-006.

The results of that study demonstrated that 82.1% of study subjects (90% confidence interval from 72% to 90%; $p = 0.3272$) could not distinguish between the JZP-258 and placebo formulations later used for that study.

The null hypothesis for this study postulated that $\geq 85\%$ of study subjects could not distinguish between JZP-258 and placebo.

While the results of that study failed to reject the null hypothesis, the sponsor did conclude that those results supported the use of that placebo formulation in Study 15-006.

11. Additional Safety Data Supporting Current Application

As JZP-258 has not been approved, no post-marketing safety data is available for Xyrem®.

Thus, the only other source of safety data for JZP-258 is that for Xyrem.

As per the sponsor:

- JZP-258 and Xyrem have the same active moiety.
- Xyrem has a “well-established safety profile supported by more than 16 years of marketed use and extensive post-marketing exposure of > (b) (4) patient-years.”
- Safety data for Xyrem is thus the most appropriate source for safety data to supplement that obtained with JZP-258 itself.

The safety data for Xyrem is, in turn, best obtained from

- The latest Periodic Benefit-Risk Evaluation Report for Xyrem®, covering the period from October 13, 2018, through October 12, 2019. This report contains cumulative safety data.
- The current Prescribing Information for Xyrem (October 2018).

Both the above have already been reviewed by me.

12. Review Of Proposed Prescribing Information And Related Documents

I have reviewed the Prescribing Information proposed by the sponsor together with the sponsor 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 finalized versions of the documents listed above that are to accompany the approval letter for this application.

Please note that the Prescribing Information for Xyrem was revised while this application was under review; that revision was made in response to a Prior Approval Labeling Supplement for Xyrem submitted under NDA 21196 (S-33) on July 15, 2020. The objective of that revision was to align the Prescribing Information for both Xyrem® and JZP-258. I am in agreement with the finalized version of the revised Prescribing Information for Xyrem®.

Dr. Tracy Peters who is affiliated with this Division as an Associate Director, has had played a primary role in drafting both the Prescribing Information and related documents. She has also had a role in the drafting of the Risk Evaluation and Mitigation Strategy (REMS).

13. Risk Evaluation And Mitigation Strategy (REMS)

In this submission, the sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) for JZP-258 which is to be combined with the existing REMS for Xyrem.

The proposed REMS has been reviewed primarily by the staff of the Division of Risk Management of the Office of Surveillance and Epidemiology.

Dr. Sally Jo Yasuda of this Division has also been closely involved with the review of that REMS.

The REMS itself is comprised of multiple documents.

Please note that the existing REMS text for Xyrem was revised while this application was under review; that revision was made in response to a Prior Approval Labeling Supplement for Xyrem submitted under NDA 21196 (S-34) on July 17, 2020. The objective of that revision was to align the Prescribing Information for both Xyrem and JZP-258. Dr. Abou-Sayed's review completed on July 17, 2020, addressed that supplement as well.

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

14. Summary Of Statistical Review

The primary statistical review of this sNDA has been performed by Dr. Xiaorong (Sharon) Yan of the Division of Biometrics I. Her review was completed on June 23, 2020.

Her review has been directed at the efficacy results of the randomized, double-blind, placebo-controlled, withdrawal phase of Study 15-006, as derived from the analysis of the primary and key secondary efficacy endpoints for that study.

She has concluded that Study 13-005 has provided sufficient evidence that Xyrem is effective as compared with placebo in treating cataplexy in patients with narcolepsy. She has also substantiated the sponsor's main analysis of the Epworth Sleepiness Scale data for that study.

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

15. Summary Of Nonclinical Review

Dr. Melissa Banks-Muckenfuss was the primary nonclinical (pharmacology-toxicology) reviewer of this New Drug Application. Her review was completed on June 8, 2020.

Dr. Banks-Muckenfuss has noted the following:

- This application has been primarily supported by cross-reference to the nonclinical pharmacology, nonclinical pharmacokinetics, and toxicology sections of NDA 21196 for Xyrem.
- The sponsor has also conducted and submitted the results of the following studies of JZP-258, all in dogs: a pharmacokinetic study, a dose-ranging

toxicology study, and a 3 month repeated-dose toxicology study (conducted according to Good Laboratory Practices). The results of those studies, which she has summarized, indicate that the toxicities of JZP-258 are similar to those of sodium oxybate alone.

She has stated that there is no objection to the approval for JZP-258 for the treatment of cataplexy or excessive daytime sleepiness in narcolepsy in adults and children, aged 7 years and older.

She has recommended that the nonclinical sections of the current Xyrem Prescribing Information be used for the Prescribing Information for JZP-258.

Please see the full text of her review for more details.

16. Summary Of Clinical Pharmacology Review

This application was reviewed by an Office of Clinical Pharmacology team comprising Drs. Gopichand Gottipatti, Sreedharan Sabarinath, and Atul Bhattaram.

The above review team recommended that this application be approved for the indication proposed by the sponsor.

A key additional recommendation from the same review team was that the first nightly dose of JZP-258 be administered at least two hours after food, similar to the dosing recommendations for Xyrem. (b) (4)

17. Summary Of Quality Assessment (Chemistry) Review

The primary quality (chemistry) assessment team for this application is comprised of Drs Gaetan Ladouceur, Grace Chiou, Joanne Wang, and Hemlata Tamta. The review was signed by Dr. Martha Heimann, the Application Team Lead, on June 3, 2020.

The quality assessment team recommended that this application be approved.

An item that was much discussed during the review of this application was the description of the potency of the drug product in the Prescribing Information. A description of that discussion is on Page 6 of the review.

Please see the full text of this review for more details about the chemistry aspects of this application.

18. Summary Of Office Of Surveillance And Epidemiology Reviews

Two reviews of this application have been completed by the staff of the Office of Surveillance and Epidemiology. These reviews are described further below.

18.1 Review By Division Of Risk Management (DRM)

Dr. Yasmeen Abou-Sayed of DRM has completed a review of the Risk Evaluation and Mitigation Strategy (REMS) proposed for JZP-258 under this application. Her review was completed on July 17, 2020, and contained a full list of the REMS-related documents that she has reviewed. In her review, she had made comments and revisions to the REMS-related documents; her comments included those that were to be conveyed to the sponsor.

Earlier reviews by Dr. Abou-Sayed were completed on June 30, 2020, and July 2020.

As already noted, the existing REMS text for Xyrem was revised while this application was under review; that revision was made in response to a Prior Approval Labeling Supplement for Xyrem submitted under NDA 21196 (S-34) on July 17, 2020. The objective of that revision was to align the Prescribing Information for both Xyrem and JZP-258. Dr. Abou-Sayed's review, completed on July 17, 2020, addressed that supplement as well.

Please see the contents of Dr. Abou-Sayed's reviews above for more details.

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

Dr. Justine Kalonia of DMEPA has completed a series of reviews of this application: these are dated: June 11, 2020; June 17, 2020; and June 24, 2020. Her reviews describe the items that she has reviewed (these include, but are not limited to, a Human Factors Development Plan) and list her comments and recommendations regarding the Prescribing Information (including the Medication Guide and Instructions for Use) for JZP-258. Her comments and recommendations have been taken into consideration by this Division while finalizing those documents.

Please see Dr. Kalonia's reviews for more details.

19. Patient Labeling Review

A Patient Labeling Review for this application was completed by Lonice Carter, MS, RN, CNL, a reviewer in the Division of Medical Policy Programs, together with Rebecca Falter, PharmD, of the Office of Prescription Drug Promotion. Her review was focused on the Medication Guide and Instructions for Use, and was

completed on July 7, 2020. Her comments and recommendations have been taken into consideration by this Division while finalizing those documents.

Please see the contents of Ms. Carter's reviews for more details.

20. Summary Of Office Of Prescription Drug Promotion (OPDP) Reviews

Two reviews have been completed by Rebecca Falter, PharmD, Regulatory Review Officer in that Office.

A review completed on June 26, 2020, has responded to a consultation from the Division of Risk Management (DRISK) for a review of the draft Risk Evaluation and Mitigation Strategy (REMS) materials accompanying this application. A number of comments and recommendations regarding those materials was made in that review and conveyed to that Division.

A second review also completed on July 7, 2020, had responded to a consultation from this Division regarding the proposed Prescribing Information, Medication Guide, and Instructions for Use (as well as container and carton labeling) accompanying this application. That review had been combined with the review from the Office of Medical Policy Programs (by Lonice Carter, MSN), described above, and a number of recommendations made regarding these labeling components.

21. Controlled Substances Staff Review

A review of this application by Chad Reissig, PhD, of the Controlled Substances Staff was completed on June 21, 2020.

His conclusions are as follows.

- JZP-258 has the same active pharmacological ingredient as Xyrem®, and in an equivalent amount.
- Since JZP-258 has a slightly higher T_{max} and a lower C_{max} as compared with Xyrem, the abuse potential of the former is not increased relative to the latter.
- Clinical studies of JZP-258 do not produce an adverse event profile indicative of a higher abuse potential than Xyrem.
- The labeling for JZP-258 is appropriate and is similar to that for Xyrem.

Based on the above, he has recommended that JZP-258 be controlled in Schedule III of the Controlled Substances Act.

Please see the full text of his review for further details.

22. Pediatric Labeling Review

Carolyn Yancey, MD, MPH, of the Division of Pediatric and Maternal Health had reviewed the Prescribing Information for this application. Her review was completed on May 28, 2020.

Dr. Yancey had reviewed Section 1 (Indications and Usage), Section 2.2 (Pediatric Dosing Information), and Section 8.4 (Pediatric Use Information) of the draft Prescribing Information for Xywav and made labeling recommendations. Those recommendations were taken into consideration by this Division when finalizing labeling.

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

23. Financial Disclosure Information

Financial disclosure information has been collected only for the single clinical efficacy trial, 15-006, included in this submission.

23.1 Components Of Certification

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

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in this study. In regard to this list the sponsor 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 required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor 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).

23.1.2 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests (FDA Form 3455)

The sponsor has listed three investigators to whom such certification applied:

(b) (6)

Further, the sponsor has cited a number of reasons why those investigators were cleared for participation in Study 15-006 and why their participation in that study was appropriate and was unlikely to have introduced significant bias into the results of the study.

23.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the single clinical study (13-005) that were submitted with this application.

24. Site Inspection Report

Two clinical sites in the United States (#s 1356 and 1454) participating in Study 15-006 were identified for Good Clinical Practice inspections via a discussion between staff of this Division, Dr. Sharon Yan of the biometrics review staff, and staff of the Good Clinical Practice Assessment Branch of the Office of Scientific Investigations.

Plans to inspect the above sites were scheduled. However, a result of the covid-19 pandemic, and the attendant risk to Agency staff conducting those inspections, plans for the above inspections were re-evaluated by this Division together with the Office of Scientific Investigations: it was then concluded that the assessment of this application could proceed without the aforementioned inspections.

A memorandum from Dr. Cara Alfaro of the Office of Scientific Investigations, states that the same Office would, as a result, not be able to determine whether the study data were reliable in support of this application.

The above site inspections are not critical to the review of this application.

25. Pediatric Waiver

The sponsor sought a waiver of pediatric studies for JZP-258 on the basis of several regulations applicable to the orphan drug designation for oxybate.

The full text of the sponsor's request for a waiver of pediatric studies is in Section 1.9.1 of this submission. Extracts of that text are copied below in italics.

Reference is made to Jazz Pharmaceuticals' orphan drug, sodium oxybate, which was designated (#94-858) pursuant to section 526 of the Federal Food,

Drug, and Cosmetic Act (21 USC 360bb) on November 7, 1994 for "treatment of narcolepsy".

The Pediatric Research Equity Act (Public Law 108-155) states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526."

FDA Guidance For Industry: How to Comply with the Pediatric Research Equity Act states: "FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time."

In alignment with the aforementioned references and because orphan designation is applicable to JZP-258, the sponsor is not obligated to submit a pediatric assessment nor is it required to submit a waiver for pediatric studies.

26. Overall Conclusion

The sponsor has provided substantial evidence of the efficacy of JZP-258 in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. The safety of the product is acceptable for the proposed indication.

27. Recommendation

I recommend that JZP-258 be approved for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm
cc:
HFD-120
IND

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

/s/

RANJIT B MANI
07/21/2020 05:24:27 PM

ERIC P BASTINGS
07/21/2020 05:38:29 PM
I concur, and will issue an approval letter for this application.