CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 212,690
Drug Name:	JZP-258
Indication(s):	Narcolepsy
Applicant:	Jazz Pharmaceuticals
Date(s):	Date of Submission: January 21, 2020 PDUFA Date: July 21, 2020
Review Priority:	Priority Review
Biometrics Division:	Division I
Statistical Reviewer:	Sharon Yan, PhD
Concurring Reviewers:	Kun Jin, PhD, Team Leader Jim Hung, PhD, Director
Medical Division:	Neurology I
Clinical Team:	Ranjit Mani, MD, Clinical Reviewer and Team Leader Eric Bastings, MD, Director
Project Manager:	Vandna Kishore, PharmD

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1 EXECUTIVE SUMMARY

This NDA application for ZEPOSIA™ (ozanimod) is seeking approval for the following indications:

> *JZP-258 is being developed to provide the same treatment benefits as Xyrem (i.e., treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy) with 92% less sodium.*

The efficacy of JZP-258 is based on a single pivotal phase 3 study 15-006, which is a double-blind, placebo-controlled, randomized-withdrawal study.

Study 15-006 demonstrated the clinical efficacy of JZP-258 in the treatment of cataplexy in patients with narcolepsy. Subjects randomized to placebo during the double-blind randomized withdrawal period experienced a significant increase (i.e., worsening) in the weekly number of cataplexy attacks compared with subjects randomized to continue treatment with JZP-258. The median change in the weekly cataplexy attacks was 2.35 for the placebo group compared with 0.00 change for the JZP-258 group with a p-value < 0.0001.

Subjects randomized to placebo during the double-blind randomized withdrawal period experienced a significant increase in Epworth Sleepiness Scale (ESS) score (i.e., worsening of excessive daytime sleepiness) compared with subjects randomized to continue treatment with JZP-258. The median change from the end of the stable dose period to the end of the double-blind withdrawal period in the ESS score was 2.0 for the placebo group compared with 0.0 change for the JZP-258 group with a p-value < 0.0001.

2 INTRODUCTION

2.1 Overview

JZP-258 was being developed for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy 7 years of age and older.

Currently, Xyrem (sodium oxybate) oral solution is the only FDA approved therapy for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy 7 years of age and older. JZP-258, developed by Jazz Pharmaceuticals, has the same active moiety as Xyrem with substantially lower sodium content compared with approved dosage of Xyrem. By formulating oxybate with a mixture of cations (calcium, potassium, magnesium, and sodium), Jazz developed JZP-258 to have 92% less sodium than Xyrem: 87 to 131 mg versus 1100 to 1638 mg in the anticipated dose range of 6 to 9 g nightly, to provide narcolepsy patients with the safety benefit of reduced sodium content and similar efficacy as Xyrem.

Study 15-006 was designed as a 2-part study consisting of a Main Study (a double-blind,

placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of JZP-258) followed by an optional 24-week open-label extension (OLE) study.

The primary endpoint of Study 15-006 was the change in the average weekly number of cataplexy attacks from the 2 weeks of the Stable Dose Period (SDP) to the 2 weeks of the Double-blind randomized-withdrawal period (DB RWP). The key secondary endpoint was the change in the ESS score from the end of the SDP to the end of the DB RWP.

The following table presents a summary of the studies included in this review.

Table 1 List of All Studies Included in This Review

	Phase and Design	Treatment Period	Comparator	# of Subjects randomized	Study Population
Study 15-006	Phase 3, double-blind, placebo-controlled, randomized-withdrawal trial	12-week open-label optimization, 2-week stable dose, 2-week randomized withdrawal	Placebo	65 to placebo; 69 to JZP-258	Patients with cataplexy and EDS

Source: Reviewer's summary

2.2 Data Sources

Original submission 1/21/2020: \\CDSESUB1\evsprod\NDA212690\0001

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No notable issues were identified in the submission of data and study documents.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of Efficacy for Protocol RPC01-301

3.2.1.1 Study Design

The Main Study (the efficacy part) of Study 15-006 was a double-blind, placebo-controlled, multicenter, randomized-withdrawal study of the efficacy and safety of JZP-258.

The Main Study consisted of 4 study periods as described below and in Figure 1.

The Screening Period lasted up to 30 days and subjects were allowed to be rescreened.

Optimized Treatment and Titration Period (OL OTTP): During the 12-week OL OTTP, eligible subjects were transitioned to JZP-258 treatment based on their pretreatment status as follows:

- Pre-randomization Group 1 (subjects receiving a stable dose of Xyrem only for at least 2 months prior to screening): Subjects were switched from Xyrem to JZP-258 (gram for gram) and remained on this JZP-258 dose for a minimum of 2 weeks. If needed, the dose of JZP-258 could be titrated during the subsequent 8 weeks to a stable, tolerable, and effective dose.
- Pre-randomization Group 2 (subjects receiving a stable dose of Xyrem and an additional anticataplectic for at least 2 months prior to screening): Subjects were switched from Xyrem to JZP-258 (gram for gram) and remained on this JZP-258 dose for a minimum of 2 weeks. Following this 2-week period, subjects were tapered off the additional anticataplectic over a minimum period of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 could be further titrated to a stable, tolerable, and effective dose during this 8-week period.
- Pre-randomization Group 3 (subjects receiving a non-Xyrem anticataplectic and not Xyrem at screening): Subjects were titrated to a tolerable dose of JZP-258 over a minimum of 2 weeks at the start of this period. After initial JZP-258 titration, subjects were tapered off other anticataplectics over a minimum of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 could be further titrated to a stable, tolerable, and effective dose during this 8-week period.
- Pre-randomization Group 4 (subjects not receiving treatment with an anticataplectic at screening): Subjects were initiated and titrated with JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during this period.

All subjects were to be treated with JZP-258 alone for the final 2 weeks of this 12-week period.

Open-Label Stable Dose Period (OL SDP): Subjects had to be titrated or converted to a tolerable and effective dose of JZP-258 alone for at least 2 weeks prior to entering the 2-week Stable Dose Period. During the 2-week SDP, subjects were to remain on the stable JZP-258 dose, unchanged, for 2 weeks. The baseline number of weekly cataplectic attacks and baseline EDS scores, as well as other secondary endpoints, were evaluated during this period.

Double-Blind Randomized-Withdrawal Period (DB RWP): Subjects were then eligible to enter the Double-blind Randomized-withdrawal Period (DB RWP) if the dose of JZP-258 remained unchanged during the SDP and, in the judgment of the investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events (AEs) due to JZP-258 treatment had occurred and subjects completed daily dosing and cataplexy diaries in the SDP.

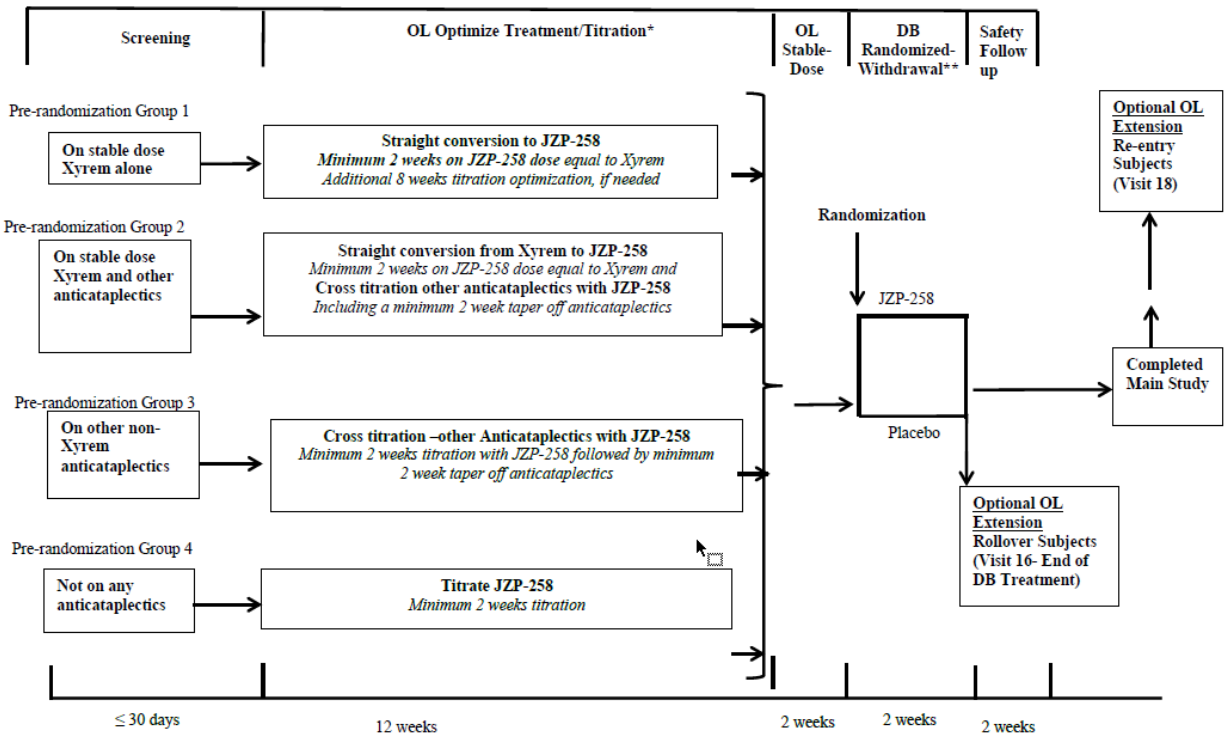
Subjects eligible to enter the DB RWP were randomized 1:1 to receive 1 of the following 2 treatments during the 2-week DB RWP:

- JZP-258: JZP-258 was continued as a double-blind treatment at the stable dose taken in the prior 2 weeks.

- JZP-258 placebo: Placebo was initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken in the prior 2 weeks.

Randomization was stratified based on each subject's pre-randomization group, as defined above.

The study enrolled male and female subjects between 18 and 70 years of age who had a primary diagnosis of narcolepsy with cataplexy and had a history of having at least 14 cataplexy attacks in a typical 2-week period and clinically significant symptoms of excessive daytime sleepiness (EDS) prior to any narcolepsy treatment.



*Titration to optimal clinical benefit, with adequate control of cataplexy and EDS while maintaining tolerability per Investigator judgment.
Subjects must be maintained on an unchanged, tolerable, and effective dose of JZP-258 for at least 2 weeks prior to entering the Stable-Dose Period.
** 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.

Figure 1 Study Diagram for Main Study (source: Figure 1 of Protocol)

3.2.1.2 Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the change in average weekly number of cataplexy attacks from the 2 weeks of the open-label SDP to the 2 weeks of the DB RWP.

Subjects were to complete a daily Cataplexy Frequency Diary each night prior to bedtime. Subjects were to record the number of cataplexy attacks that they had each day from the beginning of OTTP through the end of the DB RWP. Subjects were to complete the Cataplexy Frequency Diary on at least 10 out of the 14 days in the SDP occurring prior to the start of the DB RWP, or they were to be discontinued from the study.

Key Secondary Endpoint

The key secondary efficacy endpoint was the change in Epworth Sleepiness Scale (ESS) score from the end of the OL SDP to the end of the DB RWP.

ESS was a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses ranged from 0=would never doze to 3=high chance of dozing. Subjects were asked to complete the ESS regarding the level of sleepiness they experienced over the past 7 days at end of the SDP and at the end of the DB RWP or Early Termination from the DB RWP. The ESS total score was the sum of the 8 item-scores and ranged between 0 and 24. Higher scores indicated greater daytime sleepiness.

3.2.1.3 Statistical Methodologies

The efficacy population (EFF) was to contain all randomized subjects who had received at least one dose of DB study drug and had at least one set of post-randomization efficacy data.

3.2.1.3.1 Analyses of the Primary Endpoints

For subjects with at least one day of cataplexy attack data, the average weekly number of cataplexy attacks over each of the two weeks of the OL SDP was to be calculated as follows:

$$\frac{\text{Total number of cataplexy attacks within the OL SDP period}}{\text{Number of days with non-missing data within the OL SDP period}} \times 7 \text{ days}$$

Average weekly number of cataplexy attacks over each of the two weeks of the DB RWP was to be calculated similarly.

For the primary efficacy endpoint, an analysis of covariance (ANCOVA) was to be performed using the PROC GLM SAS procedure. The model was to include the change in average weekly number of cataplexy attacks from the two weeks of the OL SDP to the two weeks of the DB RWP as the dependent variable; the treatment group and Pre-randomization Group (Refer to Section 3.2.1.1) as fixed effects as well as the average weekly number of cataplexy attacks over the 2 weeks of the OL SDP as a covariate.

The normality assumption of the ANCOVA model was to be examined by residual analysis using the Shapiro-Wilk test at a 0.05 significance level. If the normality assumption was considered violated, a non-parametric ANCOVA with the covariate and response variables

replaced by their ranks was to be used as the primary efficacy analysis. P-values was to be presented from the rank based ANCOVA. Location shift between the change in the average weekly number of cataplexy attacks between the two treatment groups and asymptotic 95% confidence intervals was to be presented using the Hodges-Lehman estimator (Hodges and Lehman 1962).

3.2.1.3.2 Analysis of Secondary Endpoints

The ESS total score was to be analyzed similarly to the primary efficacy endpoint.

3.2.1.3.3 Handling of Missing Data

For subjects without post-randomization daily cataplexy attack data, the average weekly number of cataplexy attacks from the OL SDP was to be carried forward using a baseline observation carry forward (BOCF) approach.

For ESS total score, if three or more item scores were missing at a specific time point, the ESS total score was to be set to missing. If one or two ESS item scores were missing at a specific time point, the mean of the remaining seven or six non-missing ESS item scores at that time point was be used to impute the missing ESS item scores. The ESS total score was to be then calculated as the sum of the observed and imputed item scores.

For subjects without post-randomization ESS data, the result form the OL SDP was to be carried forward using a BOCF approach.

3.2.1.3.4 Multiplicity Consideration

The primary endpoint was to be tested first at a 2-sided significance level of 0.05. If the primary endpoint reached statistical significance, the key secondary endpoint was to be tested at the 2-sided significance level of 0.05; otherwise the key secondary endpoint was not to be tested.

3.2.1.4 Study Patients

3.2.1.4.1 Patient Disposition

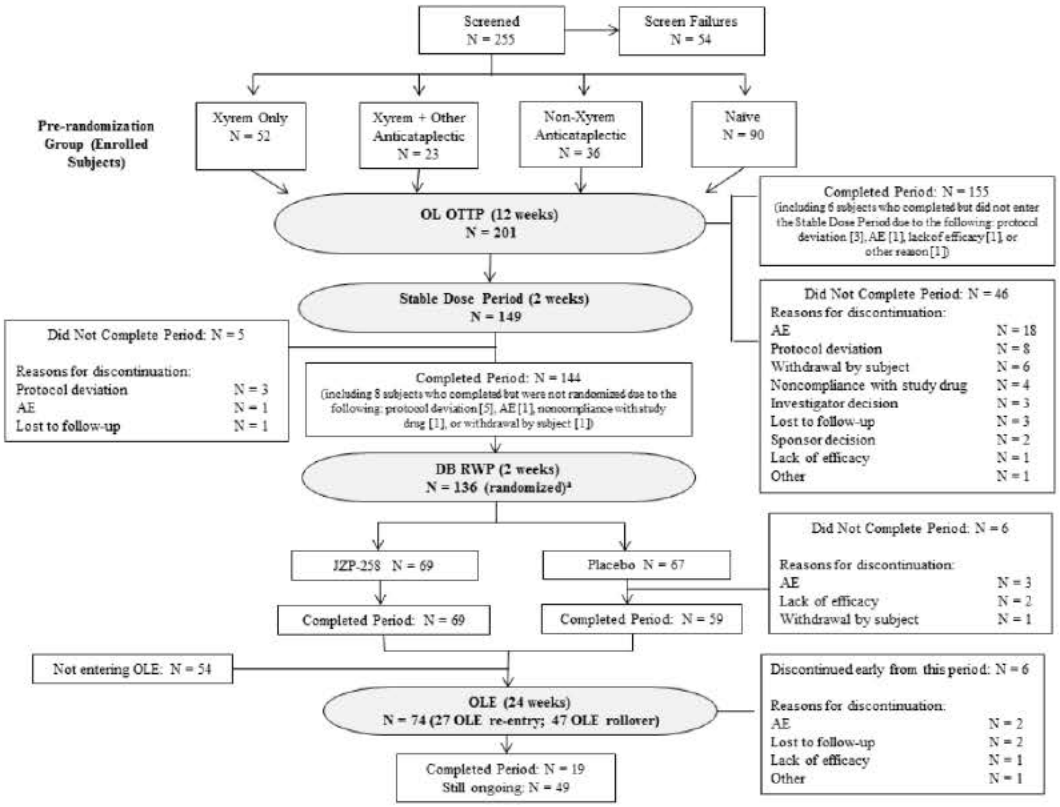
A total of 225 subjects were screened and of these, 201 subjects entered the OL OTTP and received at least 1 dose of study drug.

Subjects were treated with JZP-258 without other anticataplectic for at least the final 2 weeks of this 12-week OTTP. A total of 149 subjects overall achieved a tolerable and efficacious dose of JZP-258 and entered the OL SDP.

After completing the OL SDP, 136 subjects were randomized, but two subjects were randomized in error and did not receive any dose of study drug in the DB RWP. Therefore, 134 subjects received at least 1 dose of study drug in the DB RWP (69 subjects in the JZP-258 group and 65 subjects in the placebo group), which comprised of Efficacy Population.

Overall, a total of 5 subjects discontinued from the SDP, 8 subjects completed the SDP but were not randomized, 2 subjects who were randomized in the DB RWP in error and did not receive a dose of double-blind study drug, and 6 subjects discontinued from the DB RWP.

A summary of patient disposition is presented in Figure 3.



AE = adverse event, DB RWP = Double-blind Randomized-withdrawal Period, OLE = Open-label Extension, OL OTTP = 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.
[a] Subjects (b) (6) and (b) (6) were randomized in error and did not take study drug in the DB RWP.
Source: Tables 14.1.1.1, 14.1.1.2, and Posthoc Table 14.1.1.100; Listing 16.2.1.1

Figure 2 Disposition of Subjects (Source: CSR)

3.2.1.4.2 Patient Demographics

Demographic and baseline characteristics are summarized for the Efficacy Population in Table 2. Overall, baseline demographic characteristics were generally balanced between treatment groups in the Efficacy Population.

Table 2 Demographic Characteristics of Efficacy Population

	JZP-258 N=69	Placebo N=65
Age (years)		
Mean (SD)	37.2 (11.79)	37.8 (12.69)
Median	39.0	35.0
Sex, n (%)		
Male	26 (37.7)	26 (40.0)
Female	43 (62.3)	39 (60.0)
Race, n (%)		
White	64 (92.8)	59 (90.8)
Other and Not Reported	5 (7.2)	6 (9.2)
Region, n (%)		
North America	23 (33.3)	23 (35.4)
Europe	46 (66.7)	42 (64.6)

Source: Table 7 of CSR

3.2.1.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were similar between treatment groups in the Efficacy Population. On average, subjects had been diagnosed with narcolepsy for 8.4 and 6.8 years in the JZP-258 and placebo groups, respectively (Table 3).

Table 3 Disease History (Efficacy Population)

	JZP-258 N=69	Placebo N=65
Time since diagnosis (years)		
Mean (SD)	8.4 (8.46)	6.8 (5.63)
Median	5.6	5.8
Past symptoms prior to treatment, n (%)		
Cataplexy	69 (100.0)	65 (100.0)
EDS	69 (100.0)	65 (100.0)
Hypnagogic hallucinations	38 (55.1)	42 (64.6)
Sleep paralysis	41 (59.4)	42 (64.6)
Disrupted nighttime sleep	43 (62.3)	44 (67.7)
Current symptoms of narcolepsy, n (%)		
Cataplexy	66 (96.7)	60 (92.3)
EDS	67 (97.1)	63 (96.9)
Hypnagogic hallucinations	27 (39.1)	27 (41.5)
Sleep paralysis	29 (42.0)	23 (35.4)
Disrupted nighttime sleep	40 (58.0)	37 (56.9)

Source: Table 9 of CSR

3.2.1.5 Efficacy Results

3.2.1.5.1 Primary Endpoint – Cataplexy Attacks

At baseline (2 weeks of the Stable Dose Period), the median average weekly number of cataplexy attacks was similar between the JZP-258 and placebo groups (1.08 and 1.00, respectively). During the DB RWP, the average weekly number of cataplexy attacks increased for subjects randomized to placebo with a median change of 2.35, while the median change was 0.00 for subjects randomized to continue treatment of JZP-258. The comparison of the change from baseline between treatments was statistically significant (estimated median difference [JZP-258 – placebo]: -3.308; $p < 0.0001$).

The normality assumption of the ANCOVA model was considered violated based on prespecified criteria and a nonparametric ANCOVA with ranks was used. The median difference between the treatment groups and 95% CI were estimated with the location shift by Hodges-Lehmann method. The results of the analysis of cataplexy attacks are summarized in Table 4.

Table 4 Analysis of Change in Average Weekly Number of Cataplexy Attacks (Efficacy Population)

Average of Weekly Number of Cataplexy Attacks	**JZP-258 N=69**	**Placebo N=65**
Baseline (2 weeks of Stable Dose)		
Mean (SD)	8.91 (16.83)	7.16 (14.41)
Median	1.08	1.00
Min-Max	0.00 – 82.25	0.00 – 83.07
2 weeks of DB RWP		
Mean (SD)	9.03 (16.93)	18.63 (32.75)
Median	2.15	5.44
Min-Max	0.0 – 87.23	0.0 – 157.00
Change from Baseline		
Mean (SD)	0.12 (5.77)	11.46 (24.75)
Median	0.00	2.35
Min-Max	-23.30 – 26.12	-5.00 – 124.00
Primary analysis (non-parametric)		
Median Difference: JZP-Placebo	-3.308	
95% CI	(-6.044, -1.500)	
p-value	<0.0001	

Source: Reviewer's analysis

Altogether, 6 patients withdrew from the DB RWP, all from the placebo group. For those 6 patients, their average weekly number of cataplexy attacks was carried from baseline. This imputation assumes that their weekly cataplexy attacks were unchanged after withdrawal from the active treatment of JZP-258. Since there were no patients withdrew from patients randomized to continue JZP-258, such imputation is considered most conservative.

3.2.1.5.2 Secondary Endpoints – Excessive Daytime Sleepiness (ESS)

At the end of the 2-week SDP, the median ESS score was 13.0 for the placebo group and 14.0 for the JZP-258 group. At the end of the DB RWP, the median ESS score for subjects randomized to placebo increased by 2.0, while the median change was 0.00 for subjects randomized to continue treatment of JZP-258. The comparison of the change from baseline between treatments was statistically significant (estimated median difference [JZP-258 – placebo]: -2.000; $p < 0.0001$) from the non-parametric ANCOVA with ranks. The results of the analysis of ESS scores are summarized in Table 5.

Table 5 Change in ESS Score from the End of Stable-Dose Period to End of Double-Blind Withdrawal Period - Efficacy Population

	JZP-258 N=69		**Placebo N=65**
Baseline (End of Stable Dose)			
Mean (SD)	13.62 (5.25)		12.57 (5.46)
Median	14.0		13.0
Min, Max	3 - 24		
End of DB RWP			
Mean (SD)	13.64 (4.66)		15.58 (4.88)
Median	14.0		16.0
Min, Max	4 - 24		
Change from Baseline			
Mean (SD)	0.01 (2.90)		3.02 (4.68)
Median	0.0		2.0
Min, Max	-9, 7		-6, 20
Primary analysis (non-parametric)			
Median Difference: JZP-Placebo		-2.00	
95% CI		(-4.00, -1.00)	
p-value		<0.0001	

Source: Reviewer's analysis

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Ranjit Mani for evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analyses of the primary endpoint on subpopulations of sex and age group were performed. Age was grouped by $\leq$ 38 years and > 38 years, where 38 was the median age. Almost all patients were white and thus analysis by race was not performed.

Patients in each of the individual European countries were in small numbers and therefore, countries were pooled into two regions of Europe and USA.

Regardless of sex, age, or region, patients who were randomized to placebo had experienced an increase of at least 1 cataplexy attack in weekly median after withdrew from JZP-258, while patients who randomized to continue treatment with JZP-258 saw no change in their weekly number of cataplexy attacks. A summary of results is presented in Table 6.

Table 6 Analysis of Average Weekly Cataplexy Attacks by Subgroups of Sex, Age Group and Region (Efficacy Population)

Median of Average of Weekly Number of Cataplexy Attacks	**JZP-258 N=69**	**Placebo N=65**
Sex		
Male		
N	26	26
Baseline	1.12	0.68
Change	0.00	1.07
Median Difference: JZP-Placebo	-2.72	
(95% CI)	(-5.44, 0.00)	
Female		
N	43	39
Baseline	1.08	1.62
Change	0.00	2.55
Median Difference: JZP-Placebo	-4.94	
(95% CI)	(-8.12, -1.77)	
Age Group		
≤ 38 ears		
N	31	37
Baseline	1.08	1.40
Change	0.00	4.71
Median Difference: JZP-Placebo	-5.45	
(95% CI)	(-9.22, -1.70)	
> 38 years		
N	38	28
Baseline	1.88	0.52
Change	0.00	1.56
Median Difference: JZP-Placebo	-2.63	
(95% CI)	(-4.85, -0.42)	
Region		
USA		
N	23	23
Baseline	1.00	1.00
Change	0.10	2.06
Median Difference: JZP-Placebo	-3.50	
(95% CI)	(-7.00, 0.00)	
Europe		
N	46	42
Baseline	2.75	1.04
Change	0.00	2.37
Median Difference: JZP-Placebo	-4.82	
(95% CI)	(-7.85, -1.79)	

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

Efficacy of the primary endpoint by pre-randomization group was analyzed. Patients who were randomized to placebo group experienced an increase in cataplexy attacks after withdrew from JZP-258 treatment while patients who continued JZP treatment had generally no change in cataplexy attacks, independent of their pre-randomization status (Table 7).

Table 7 Average Weekly Cataplexy Attacks by Pre-randomization Group

Median of Average of Weekly Number of Cataplexy Attacks	JZP-258 N=69	Placebo N=65
Pre-Randomization Group		
Naive		
N	30	28
Baseline	1.62	0.95
Change	0.00	2.47
Median Difference: JZP-Placebo	-4.32	
(95% CI)	(-7.85, -0.80)	
Non-Xyrem		
N	11	10
Baseline	5.50	1.38
Change	0.0	6.29
Median Difference: JZP-Placebo	-15.24	
(95% CI)	(-28.68, -1.80)	
Xyrem Only		
N	22	19
Baseline	1.04	1.00
Change	0.00	1.12
Median Difference: JZP-Placebo	-1.75	
(95% CI)	(-3.50, 0.00)	
Xyrem+Other		
N	6	8
Baseline	13.50	1.06
Change	0.29	3.47
Median Difference: JZP-Placebo	-5.98	
(95% CI)	(-13.13, 1.17)	

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No notable statistical issues were identified.

5.2 Collective Evidence

Collective evidence is not evaluated since this is a single study application.

5.3 Conclusions and Recommendations

Study 15-006 has provided sufficient evidence that JZP-258 is effective as compared with placebo in reducing the number of cataplexy attacks and daytime sleepiness, regardless of patient's previous treatment for cataplexy attacks.

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/s/

XIAORONG YAN
06/23/2020 12:14:32 PM

KUN JIN
06/23/2020 03:03:15 PM
I concur with the review.

HSIEN MING J HUNG
06/23/2020 03:06:10 PM