CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s000

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 214755
Drug Name:	Sodium Oxybate ER (FT218)
Indication(s):	Narcolepsy
Applicant:	Avadel CNS Pharmaceuticals
Date(s):	Date of Submission: December 15, 2020 PDUFA Date: December 15, 2021
Review Priority:	Standard 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 Teresa Buracchio, MD, Deputy Director Eric Bastings, MD, Director
Project Manager:	Teresa Wheelous, PharmD

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1 EXECUTIVE SUMMARY

Sodium oxybate is a marketed treatment used for cataplexy and excessive daytime sleepiness (EDS) in narcolepsy. Avadel's product, FT218 (LUMRYZ), similarly contains sodium oxybate but in an extended-release formulation, has been developed to deliver the same amount of sodium oxybate to marketed product of Xyrem® in a single dose at bedtime.

This NDA application for LUMRYZ is seeking approval for the following indications:

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

The clinical efficacy of FT218 for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy is based on one Phase 3 trial, CLFT218-1501.

CLFT218-1501 was a multicenter, randomized, double-blind, and placebo-controlled study. Two populations (NT1 and NT2) of narcoleptic subjects were studied in a single parallel group 2-arm design to compare the efficacy of 6 g, 7.5 g, and 9 g of FT218 to placebo for the treatment of cataplexy and EDS. A total of 222 patients were randomized.

All three doses of FT218 were significantly more efficacious than placebo measured by co-primary endpoints of Maintenance Wakefulness Test (MWT) and Clinical Global Impression of Change (CGI-C) for EDS and by the primary endpoint of the number of cataplexy attacks (NCA) for cataplexy with p-values <0.001. The selected FT218 doses of 6.0, 7.5, and 9.0 g match the therapeutic dose range recognized for the reference drug product, Xyrem.

2 INTRODUCTION

2.1 Overview

Avadel has developed sodium oxybate extended-release oral suspension (FT218), which could be dosed once at bedtime, to provide the same level of efficacy and safety as the current, twice-nightly marketed product of Xyrem®. FT218 has been formulated as an extended-release oral suspension at concentrations of 4.5 g, 6 g, 7.5 g, and 9 g.

The efficacy of FT218 for the treatment of cataplexy and excessive daytime sleepiness (EDS) in narcolepsy is based on one Phase 3 trial, CLFT218-1501.

CLFT218-1501 was a multicenter, randomized, double-blind, and placebo-controlled study. Two populations (NT1 and NT2) of narcoleptic subjects were studied in a single parallel group design. A total of 222 patients were randomized.

The primary objectives were to compare the efficacy of 6 g, 7.5 g, and 9 g of FT218 to placebo in treating:

- EDS in both NT1 (narcolepsy with both EDS and cataplexy) and NT2 (narcolepsy with EDS but with no cataplexy) patients as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinician Global Impression (CGI) rating of sleepiness; and
- Cataplexy in NT1 narcolepsy patients as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary (SSDD).

All three doses of FT218 were significantly more efficacious than placebo in MWT, CGI-C, and NCA with p-values <0.001. The selected FT218 doses of 6.0, 7.5, and 9.0 g match the therapeutic dose range recognized for the reference drug product, Xyrem.

The following table presents a summary of the study 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
CLFT218-1501	Phase 3, randomized, double-blind, placebo-controlled	13 weeks	Placebo	Placebo: 111 FT218: 111	Two populations of narcoleptic patients

Source: Reviewer's summary

2.2 Data Sources

Supplemental NDA December 15, 2020: \\CDSESUB1\evsprod\NDA214755

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 Study CLFT218-1501

3.2.1.1 Study Design

The primary objectives of the study were:

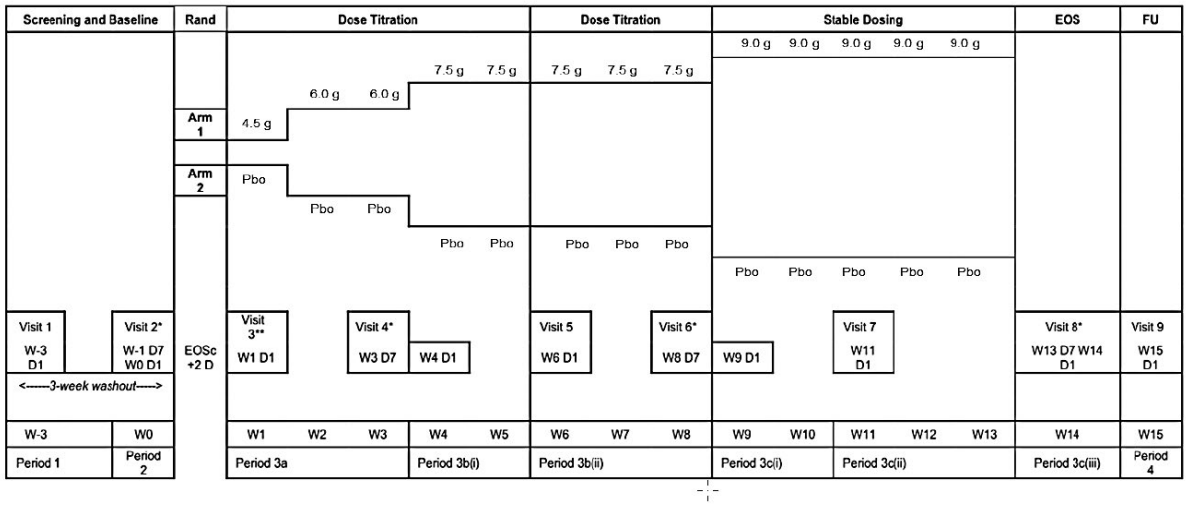
- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating EDS in both NT1 and NT2 subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness
- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary (SSDD)

This was a Phase 3 randomized, double-blind, placebo-controlled, 2-arm clinical study. Two populations of narcoleptic subjects (NT1 with both symptoms of EDS and cataplexy and the NT2 with EDS) were studied in a single parallel group design. Randomization stratified eligible subjects by narcolepsy type (NT1 and NT2) in a 1:1 ratio to treatment with either FT218 or placebo. Subjects were randomized to achieve ≥ 70 completers per arm with EDS and ≥ 50 subjects per arm with both EDS and cataplexy.

The duration of the study (screening to follow-up) was approximately 17 weeks (Figure 1). A 3-week screening period was followed by a central assessment of polysomnogram (PSG) and next-day MWT screening at Visit 2. Upon confirmation of eligibility criteria, patients were randomized while off-site, returning at Visit 3 to confirm that all entry criteria were still met and began active treatment period. A 13-week treatment period (8-week up-titration period followed by 5 weeks on stable dosing at 9.0 g/night or placebo) was followed by a 1-week follow-up period.

No study visits were affected by the Coronavirus Disease 2019 (COVID-19) pandemic while subjects were taking study drug, but the last two follow-up visits were conducted remotely.

The study schematic and schedule of assessments are presented in Figure 1.



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

Figure 1 Graphical Study Design (source: Protocol)
Source: Figure 2 of CSR

3.2.1.2 Study Endpoints

Primary Endpoints

Two subject populations were studied: the NT1 group with both narcolepsy symptoms (EDS and cataplexy) and the NT2 group with EDS.

1. *Primary Endpoints for EDS*

The co-primary endpoints for evaluating EDS in both NT1 and NT2 narcolepsy patients were mean sleep latency across 5 naps on the Maintenance of Wakefulness Test (MWT) and the Clinician Global Impression of improvement (CGI-I) for sleepiness.

The MWT was evaluated as a quantitative polysomnography (PSG) measurement of daytime wakefulness/somnolence on whether a subject was able to stay awake for a defined period of time (90-minutes between one nap ending and the next one starting, spaced at 2-hour intervals throughout the day). Sleep latency was assessed by the amount of time it took for subjects to fall asleep during the test.

The CGI-Improvement (CGI-I) was evaluated on a 7-point scale, centered at 4 (no change) and ranging from 1 (very much improved) to 7 (very much worse). Subjects were assessed relative to the severity of sleepiness at baseline by qualified and approved evaluators.

2. *Primary Endpoint for Cataplexy*

The primary endpoint for evaluating cataplexy was the number of cataplexy attacks (NCA), which was evaluated only on the narcolepsy NT1 subpopulation. The NCA was the mean number of cataplexy events recorded on the Sleep and Symptom Daily Diary (SSDD) during the dosing period.

A minimum number of diary entries of 3 per week was required for the average to be considered an observation. If the number of days with entries was less than 3, the mean NCA for that week was to be considered missing.

Secondary Endpoint

Secondary/exploratory efficacy endpoints were

1. Disturbed Nocturnal Sleep (DNS)
2. Epworth Sleepiness Scale (ESS)
3. The number of transient arousals on the nocturnal polysomnogram
4. Quality of sleep visual analogue scale (VAS)
5. Refreshing nature of sleep VAS
6. Hypnogogic Hallucination (HH)
7. Sleep Paralysis (SP)

3.2.1.3 Statistical Methodologies

The ITT population, including all randomized subjects with at least one efficacy measurement after receiving the 6 g dose (whether FT218 or placebo), was to be used for primary analyses of efficacy endpoints.

3.2.1.3.1 Analysis of the Primary Endpoints

A mixed effect repeated measures (MMRM) model was to be used to analyze the change from baseline for MWT and NCA. Each model was to include treatment, time (at which the measurement was taken), treatment-by-time interaction, pooled site and baseline score as fixed effects and subjects as random effects. Time was to range over the entire period of observations, which were taken at Visits 4, 6, and 8 for MWT and averaged over dosing periods for NCA. The analysis and the resultant F-tests were to be based on Kenward- Roger's adjusted degrees of freedom. The coefficients in the model were to be estimated by generalized least squares, with parameters estimated by restricted maximum likelihood (REML). Missing observations were considered ignorable or missing at random (MAR). Study sites were pooled into two regions of US and ex-US. Because of the possibility that some of the underlying assumptions of the proposed MMRM analysis could be violated, the p-values were to be determined by a randomization test utilizing at least 1000 replications.

For CGI, a GLIMMIX model for binomial data with logit link was to be used to analyze the categorized CGI response, i.e., proportion of patients who were very much or much improved. The model was to include treatment, time, treatment-by-time interaction and site as fixed effects and subjects as random effects. Time was to range over the entire period of observations, taken at Visits 4, 5, 6, 7, and 8. The odds ratio, 95% confidence intervals for the odds ratio and p-value were to be provided.

3.2.1.3.2 Analysis of Secondary Endpoints

Secondary/exploratory endpoints were meant to appraise the consistency of findings of effectiveness. No statistical analysis methods were specified in SAP.

3.2.1.3.3 Multiplicity Consideration

The hypothesis testing was to proceed in the following order. The sequence is presented pictorially in Figure 2.

For the hypotheses for EDS, both MWT and CGI were to be tested first. For the 9 g dose, if both tests were significant, NCA for the same dose was to be tested. If the first test failed (either MWT or CGI not significant), the null hypothesis of no treatment difference for the 9 g dose was not rejected for either symptom.

If the first test was significant for both MWT and CGI, but not for NCA, the 9 g dose was demonstrated to exceed placebo for EDS but not for cataplexy. If both tests were statistically significant, the 9 g dose had shown to be effective for EDS and for cataplexy.

If the 9 g dose demonstrated efficacy for both EDS and cataplexy, the same sequence of testing was to be followed for the 7.5 g dose using contrasts over the Periods 3b(i) and 3b(ii). If the 7.5 g dose demonstrated efficacy for both EDS and cataplexy, the same sequence of testing was to be followed for the 6 g dose using contrasts over Period 3a.

Each dose was to be tested at the two-sided alpha level of .05.

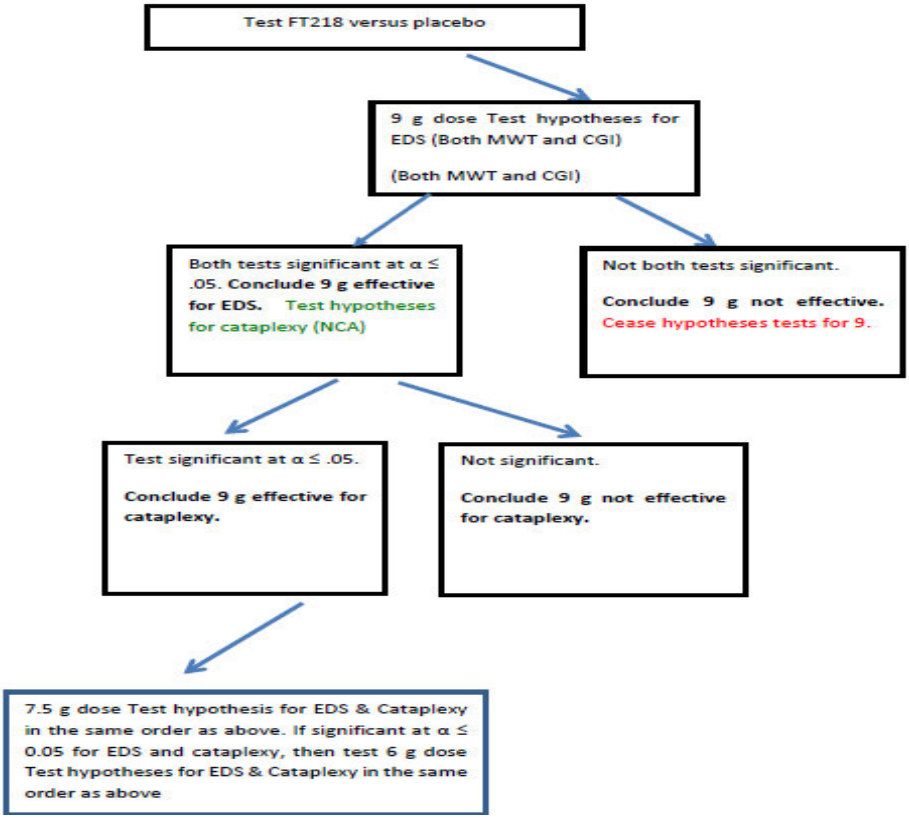


Figure 2 Sequential Testing for Comparing SOCR and Placebo
Source: Figure 1 of Statistical Analysis Plan

3.2.1.4 Study Patients

3.2.1.4.1 Patient Disposition

A total of 222 subjects were randomized. Ten of the 222 randomized patients were found ineligible for study participation after randomization and study drug was not dispensed, and 212 (95.5%) of those received at least one dose of study drug.

Overall, 148 subjects (69.8%) completed the study and 64 subjects (30.2%) prematurely discontinued. The most frequently reported reasons for premature discontinuation were AE (n = 24, 11.3%), withdrawal by subject (n = 22, 10.4%), and lack of efficacy (n = 10, 4.7%).

A summary of subject disposition is presented in Table 2 and a flow chart is presented in Figure 3.

Table 2 Subject Disposition (All Randomized Subjects)

	FT218	Placebo	Total
Randomized	111	111	222
Received at least 1 dose (MITT, Safety), n (%)	107 (96.4)	105 (94.6)	212 (95.5)
Completed study, n (%)	69 (64.5)	79 (75.2)	148 (69.8)
Discontinued study, n (%)	38 (35.5)	26 (24.8)	64 (30.2)
Adverse event	21 (19.6)	3 (2.9)	24 (11.3)
Withdrawal by subject	11 (10.3)	11 (10.5)	22 (10.4)
Lack of efficacy	2 (1.9)	8 (7.6)	10 (4.7)
Other	2 (1.9)	1 (1.0)	3 (1.4)
Pregnancy	2 (1.9)	0	2 (0.9)
Protocol deviation	0	2 (1.9)	2 (0.9)
Noncompliance	0	1 (1.0)	1 (0.5)

Source: Table 11 of CSR

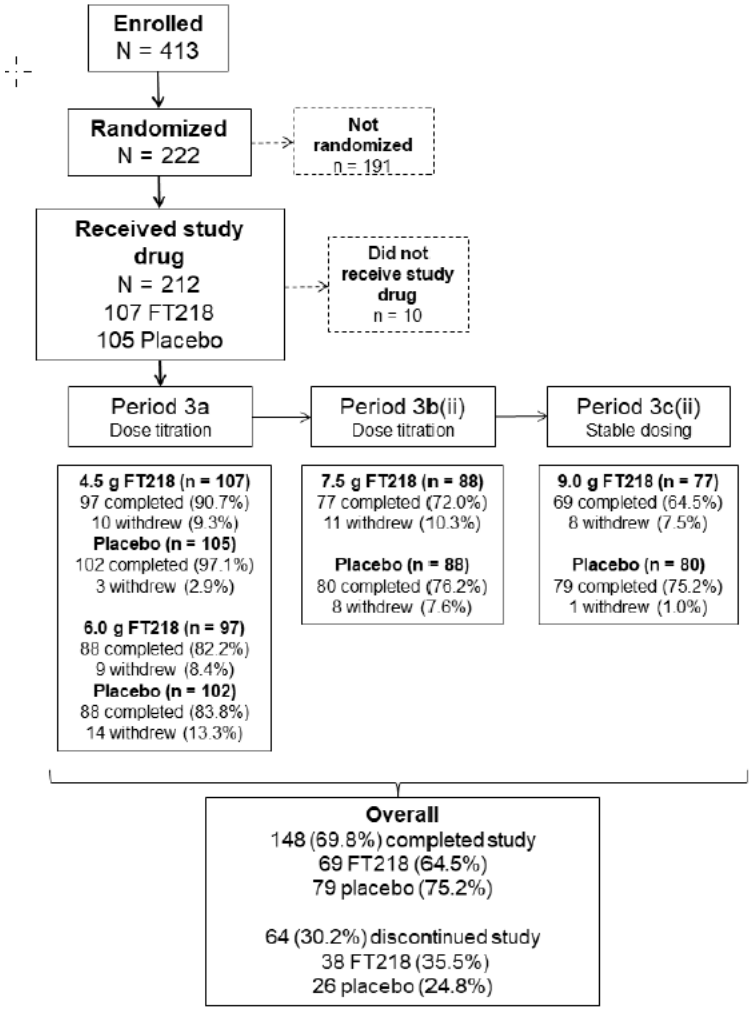


Figure 3 Subject disposition flow chart

Source: Figure 3 of CSR

3.2.1.4.2 Patient Demographics

Baseline demographic characteristics are summarized in Table 3 for the Safety Population. The treatment groups were generally balanced with respect to demographic characteristics at baseline. Overall, the mean age of the subjects was 31.2 years. More female than male subjects were enrolled (67.9% vs. 32.1%, respectively). The population comprised White subjects (n = 160, 75.5%), Black/African American (n = 36, 17.0%), Asian (n = 11, 5.2%), and small numbers of other races. Approximately 55% (n = 116) were enrolled in the US. A total of 162 subjects (76.4%) had a diagnosis of NT1 and 50 subjects (23.6%) had NT2.

Table 3 Baseline Demographic Characteristics (Safety Population)

	FT218 N=107	**Placebo N=105**
Age (years)		
Mean (SD)	30.9 (10.70)	31.6 (11.24)
Median (range)	29.0 (16-72)	30.0 (16-69)
Gender, n (%)		
Female	69 (64.5)	75 (71.4)
Male	38 (35.5)	30 (28.6)
Race, n (%)		
White	80 (74.8)	80 (76.2)
Black/African American	21 (19.6)	15 (14.3)
Asian	3 (2.8)	8 (7.6)
Other	3 (2.8)	2 (1.9)
Region, n (%)		
United States	63 (58.9)	53 (50.5)
Rest of World	44 (41.1)	52 (49.5)
Narcolepsy Type, n (%)		
NT1	80 (74.8)	82 (78.1)
NT2	27 (25.2)	23 (21.9)

Source: Table 14 of CSR

3.2.1.5 Efficacy Results

3.2.1.5.1 Analysis of Primary Endpoints

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

Analysis of MWT, Mean Sleep Latency

Nineteen (19) subjects in the FT218 group and 17 subjects in the placebo group discontinued study during the dose titration Period 3a and did not have post-baseline measure. Eighty-seven (87) subjects in the FT218 group and 88 subjects in the placebo group had both baseline MWT measure and at least one post-baseline MWT measure starting from 6 g at Visit 4 (Week 3).

At baseline, the mean MWT was similar between the two treatment groups. Beginning with Week 3 and sustained through Week 13, all three doses of FT218 had significantly better scores compared with placebo in the change from baseline in MWT (all $p < 0.0001$). It was not clear whether the increasing in the change from baseline by visit represented dose response, as claimed by the sponsor. While the dose was increased by visit, so was the treatment duration. A summary of the analysis results is presented in Table 4.

Table 4 MWT Mean Sleep Latency Change from Baseline to the End of Each Dose Period – mITT

MWT Mean Sleep Latency (minutes)	FT218 N=107	Placebo N=105
Baseline		
N	87	88
Mean (SD)	5.0 (3.13)	4.7 (2.59)
Change from Baseline to Visit 4 (Week 3), 6.0 g		
N	87	88
LS Mean (SE)	8.1 (0.75)	3.1 (0.74)
Difference to placebo (95% CI)	4.98 (2.90, 7.05)	
p-value	<0.0001	
Change from Baseline to Visit 6 (Week 8), 7.5 g		
N	76	78
LS Mean (SE)	9.6 (0.86)	3.3 (0.84)
Difference to placebo (95% CI)	6.21 (3.84, 8.58)	
p-value	<0.0001	
Change from Baseline to Visit 8 (Week 13), 9.0 g		
N	68	78
LS Mean (SE)	10.8 (0.96)	4.7 (0.92)
Difference to placebo (95% CI)	6.13 (3.52, 8.75)	
p-value	<0.0001	

Source: Reviewer's analysis confirming results from Table 18 CSR

Analysis of Clinical Global Impression of Sleepiness

Eighty-seven (87) subjects in each of the treatment group had at least one post-baseline measure for CGI. At the baseline, the CGI severity scores were balanced between the treatment groups. The CGI-I scores decreased (improved) with the increase of the dose or treatment duration for both treatment groups. The percentage of responders with much or very much improved CGI-I score increased by visit. The treatment difference measured by odds ratio of being a responder as

statistically significant (p-values < 0.0001) at Visits 4, 6, and 8 with highest odds ratio of 10.29 observed at Visit 4.

Table 5 Summary of CGI Improvement of Sleepiness by Visit - mITT

CGI Improvement	FT218 N=107	Placebo N=105
Baseline (CGI Severity)		
N	87	86
Mean (SD)	5.1 (1.14)	5.0 (1.16)
Visit 4 (Week 3), 6.0 g		
N	87	87
Mean (SD)	2.7 (0.89)	3.6 (0.87)
Number (%) of Responder	35 (40.2)	5 (5.7)
Odds ratio to placebo (95% CI)	10.29 (3.93, 26.92)	
p-value	<0.0001	
Visit 6 (Week 8), 7.5 g		
N	75	81
Mean (SD)	2.4 (0.90)	3.3 (1.10)
Number (%) of Responder	48 (64.0)	18 (22.2)
Odds ratio to placebo (95% CI)	5.67 (2.82, 11.40)	
p-value	<0.0001	
Visit 8 (Week 13), 9.0 g		
N	69	79
Mean (SD)	2.1 (0.89)	3.1 (1.07)
Number (%) of Responder	50 (72.5)	25 (31.7)
Odds ratio to placebo (95% CI)	5.56 (2.76, 11.23)	
p-value	<0.0001	

Source: Reviewer's analysis

Number of Cataplexy Attacks

Eighty (80) subjects in the FT218 group and 82 subjects in the placebo group were enrolled as NT1 subjects who had symptoms of both EDS and cataplexy attacks. At baseline, the mean NCA was similar in both treatment groups. Compared with placebo, a significantly higher mean weekly reduction in NCA was observed for all three doses of FT218, beginning at Week 3 and sustained through Week 13 (all $p < 0.0001$). Again, it was difficult to determine whether the increasing in the reduction of NCA by dose could be interpreted as dose response since as the dose increased, so did the treatment period. A summary of the analysis is presented in Table 6.

Table 6 Mean Weekly NCA by Dosing Period - NT1 Subjects in mITT

Mean Weekly NCA	FT218 N=80	Placebo N=82
Baseline		
N	73	72
Mean (SD)	18.9 (8.70)	19.8 (8.87)
Change from Baseline to Visit 4 (Week 3), 6.0 g		
N	73	72
LS Mean (SE)	-7.4 (0.79)	-2.6 (0.79)
Difference to placebo (95% CI)	-4.83 (-7.04, -2.62)	
p-value	<0.0001	
Change from Baseline to Visit 6 (Week 8), 7.5 g		
N	66	69
LS Mean (SE)	-10.0 (0.89)	-3.7 (0.88)
Difference to placebo (95% CI)	-6.27 (-8.74, -3.81)	
p-value	<0.0001	
Change from Baseline to Visit 8 (Week 13), 9.0 g		
N	55	62
LS Mean (SE)	-11.5 (0.96)	-4.9 (0.95)
Difference to placebo (95% CI)	-6.65 (-9.32, -3.98)	
p-value	<0.0001	

Source: Reviewer's analysis confirming results from Table 20 CSR

3.2.1.5.2 Secondary Endpoints

Analysis of secondary endpoints were not performed by the reviewer since no statistical methods were specified in the protocol or SAP.

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 endpoints on subpopulations of sex, age group, race, and region were performed. Age was grouped by < 30 years and ≥ 30 years, where the median age was 29. Analysis by race was summarized for White and African American only, as the number of subjects in other races were too small to make meaningful summaries.

Results from analysis of MWT and CGI in subpopulations were generally consistent with the results from the overall population (Table 7 and Table 8), except that African American subjects did not have as large benefit from the treatment of FT218 as observed in White subjects.

Table 7 Analysis of MWT by sex, age group, race and region

Change from baseline in MWT	Visit 4, 6.0 g		Visit 6, 7.5 g		Visit 8, 9.0 g	
	FT218 N=87	Placebo N=88	FT218 N=76	Placebo N=78	FT218 N=68	Placebo N=78
Sex						
Male						
N	37	27	35	25	3.52	26
LSmean of change	6.20	2.50	7.62	3.26	9.52	4.23
Difference (FT218-placebo)	3.70		4.36		5.29	
Female						
N	50	61	41	53	33	52
LSmean of change	9.46	3.27	11.07	3.25	11.62	4.81
Difference (FT218-placebo)	6.19		7.82		6.80	
Age group						
< 30 years						
N	47	45	42	40	40	40
LSmean of change	7.91	2.51	10.01	2.64	11.26	3.76
Difference (FT218-placebo)	5.40		7.37		7.49	
≥ 30 years						
N	40	43	34	38	28	38
LSmean of change	8.17	3.65	8.85	4.03	10.18	5.62
Difference (FT218-placebo)	4.52		4.82		4.55	
Race						
White						
N	65	64	54	57	48	57
LSmean of change	8.92	2.91	10.84	3.28	11.56	4.60
Difference (FT218-placebo)	6.01		7.55		6.95	
Black or African American						
N	17	14	17	13	15	13
LSmean of change	6.99	5.44	6.86	4.70	10.39	5.36
Difference (FT218-placebo)	1.55		2.16		5.02	
Region						
United States						
N	49	47	44	43	39	42
LSmean of change	8.03	2.91	8.80	2.77	11.04	4.44
Difference (FT218-placebo)	5.12		6.03		6.60	
Rest of World						
N	38	41	32	35	29	36
LSmean of change	7.97	3.26	10.46	3.97	10.62	4.82
Difference (FT218-placebo)	4.71		6.48		5.80	

Source: reviewer's summary

Table 8 Analysis of CGI by sex, age group, race and region

CGI Response Much improved or very much improved	Visit 4, 6.0 g		Visit 6, 7.5 g		Visit 8, 9.0 g	
	FT218 N=87	**Placebo N=87**	**FT218 N=75**	**Placebo N=81**	**FT218 N=69**	**Placebo N=79**
Sex						
Male						
N	37	28	33	27	35	26
Number (%) of responders	16 (43.24)	0 (0)	20 (60.61)	5 (18.52)	26 (74.29)	7 (26.92)
Odds Ratio (FT218/placebo)	>100		6.345		8.223	
Female						
N	50	59	42	54	34	53
Number (%) of responders	19 (38.00)	5 (8.47)	28 (66.67)	13 (24.07)	24 (70.59)	18 (33.96)
Odds Ratio (FT218/placebo)	5.905		5.705		4.164	
Age group						
< 30 years						
N	47	43	42	41	40	40
Number (%) of responders	17 (36.17)	2 (4.65)	29 (69.05)	10 (24.39)	33 (82.50)	14 (35.00)
Odds Ratio (FT218/placebo)	9.710		6.061		9.274	
≥ 30 years						
N	40	44	33	40	29	39
Number (%) of responders	18 (45.00)	3 (6.82)	19 (57.58)	8 (20.00)	17 (58.62)	11 (28.21)
Odds Ratio (FT218/placebo)	11.142		5.169		3.332	
Race						
White						
N	65	63	53	59	49	57
Number (%) of responders	28 (43.08)	4 (6.35)	32 (60.38)	13 (22.03)	35 (71.43)	17 (29.82)
Odds Ratio (FT218/placebo)	10.131		4.658		5.534	
Black or African American						
N	17	14	17	14	15	14
Number (%) of responders	4 (23.53)	1 (7.14)	11 (64.71)	4 (28.57)	11 (73.33)	7 (50.00)
Odds Ratio (FT218/placebo)	4.060		4.633		2.904	
Region						
United States						
N	48	46	43	44	40	43
Number (%) of responders	21 (43.75)	4 (8.70)	28 (65.12)	11 (25.00)	30 (75.00)	14 (32.56)
Odds Ratio (FT218/placebo)	7.589		4.791		6.142	
Rest of World						
N	39	41	32	37	29	36
Number (%) of responders	14 (35.90)	1 (2.44)	20 (62.50)	7 (18.92)	20 (68.97)	11 (30.56)
Odds Ratio (FT218/placebo)	20.603		6.991		4.458	

Source: reviewer's summary

Results from analysis of NCA in subpopulations of NT1 subjects were generally consistent with the results from the overall population (Table 9), except that FT218 appeared to have no effect in African American subjects.

Table 9 Analysis of NCA by sex, age group, race and region – NT1 subjects

Change from baseline in NCA	Visit 4, 6.0 g		Visit 6, 7.5 g		Visit 8, 9.0 g	
	FT218 N=73	Placebo N=72	FT218 N=66	Placebo N=69	FT218 N=55	Placebo N=62
Sex						
Male						
N	24	18	24	18	23	17
LSmean of change	-8.44	-3.55	-10.29	-4.53	-11.31	-6.21
Difference (FT218-placebo)	-4.89		-5.77		-5.10	
Female						
N	49	54	42	51	32	45
LSmean of change	-6.95	-2.22	-9.91	-3.39	-11.80	-4.34
Difference (FT218-placebo)	-4.73		-6.53		-7.47	
Age group						
< 30 years						
N	35	34	33	32	30	29
LSmean of change	-7.53	-3.22	-10.94	-4.21	-12.77	-4.73
Difference (FT218-placebo)	-4.31		-6.73		-8.04	
≥ 30 years						
N	38	38	33	37	25	33
LSmean of change	-7.27	-2.07	-8.99	-3.30	-10.18	-4.93
Difference (FT218-placebo)	-5.21		-5.69		-5.25	
Race						
White						
N	57	53	51	50	42	44
LSmean of change	-7.51	-2.66	-10.41	-3.94	-12.23	-5.21
Difference (FT218-placebo)	-4.85		-6.48		-7.03	
Black or African American						
N	13	13	12	13	10	13
LSmean of change	-3.59	-3.35	-3.69	-3.37	-3.78	-4.60
Difference (FT218-placebo)	-0.24		-0.32		0.82	
Region						
United States						
N	41	37	37	36	32	33
LSmean of change	-6.28	-2.05	-8.80	-3.41	-10.25	-3.86
Difference (FT218-placebo)	-4.23		-5.39		-6.39	
Rest of World						
N	32		29		23	
LSmean of change	-8.62	35	-11.18	33	-12.88	29
Difference (FT218-placebo)	-5.53	-3.09	-7.31	-3.88	-7.26	-5.62

Source: reviewer's summary

4.2 Other Special/Subgroup Populations

No other special/subgroup analyses were performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The rate of discontinuation was high. Overall, 64 (30.2%) subjects discontinued study prematurely, 38 (35.5%) in FT218 group and 26 (24.8%) in the placebo group. A total of 36 (17%) subjects (19 in the FT218 group and 17 in the placebo group) discontinued the study before having any post-baseline measure at Week 4. A total of 22 (10.4%) subject withdrawals, 11 in each group, was balanced by treatment and should not have an effect to favor FT218. A total of 24 (11.3%) subjects discontinued due to adverse event and 21 of them occurred in FT218 group. Given that 81% of subjects in FT218 group and 84% of subjects in the placebo group were assessed at 6 g dose level and large treatment difference at all dose levels on all 3 primary endpoints, the evidence of treatment effect is well established after taking into account of the impact of discontinuation.

5.2 Collective Evidence

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

5.3 Conclusions and Recommendations

Study CLFT218-1501 has provided sufficient evidence that FT218 is effective as compared with placebo in the treatment of cataplexy attacks and daytime sleepiness in patients with narcolepsy.

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/s/

XIAORONG YAN
09/24/2021 09:12:31 AM

KUN JIN
09/24/2021 09:20:58 AM
I concur with the review.

HSIEN MING J HUNG
09/24/2021 09:44:39 AM