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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Number: 212102 Resubmission

Drug Name: Fintepla (fenfluramine)

Indications: For the treatment of seizures associated with Dravet syndrome in patients 2 years and older

Applicant: Zogenix, Inc.

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1 EXECUTIVE SUMMARY

On September 25, 2019, Zogenix, Inc. resubmitted a new drug application (NDA) for Fintelpa (fenfluramine, or ZX008 under Zogenix, Inc.’s clinical program). The NDA resubmission contained two efficacy studies – Study 1 and Study ZX008-1504 Cohort 2 – to support the proposed indication “the treatment of seizures associated with Dravet syndrome in patients 2 years and older”. The two studies were randomized, double-blind, placebo-controlled, parallel-group studies similar in design and consisted of Baseline, Titration, and Maintenance periods. Study 1 studied 2 doses of ZX008 while Study ZX008-1504 Cohort 2 only studied one dose of ZX008. Both studies used the change in the convulsive seizure frequency per 28 days during the Titration and Maintenance periods compared with the Baseline period as the primary efficacy endpoint and the proportion with $\geq 50\%$ reduction from Baseline in convulsive seizure frequency and the longest interval between convulsive seizures as the key secondary efficacy endpoints.

Table 1. An overview of efficacy results

	Study 1			Study 1504 Cohort 2	
	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)	Placebo (N = 42)	ZX008 0.5 mg/kg/day (N = 43)
Primary endpoint: change in the convulsive seizure frequency per 28 days during the Titration and Maintenance periods compared with the Baseline period					
% difference relative to placebo	--	-31.7	-70.0	--	-59.5
p-value compared to placebo	--	0.043	< 0.001	--	< 0.001
Secondary endpoint 1: proportion with $\geq 50\%$ reduction from Baseline in convulsive seizure frequency					
Number of Subjects with $\geq 50\%$ reduction (%)	3 (7.7)	13 (34.2)	28 (70.0)	2 (4.8)	23 (53.5)
p-value compared to placebo	--	0.007	< 0.001	--	< 0.001
Secondary endpoint 2: longest interval between convulsive seizures					
Median (days)	8.0	13.0	20.5	12.0	17.0
p-value compared to placebo	--	0.043	< 0.001	--	0.010

Source: the statistical reviewer and selected from the response to information request received on March 31, 2020

Table 1 is a side-by-side presentation of the efficacy results of Study 1 and Study 1504 Cohort 2. In both studies, the ZX008-placebo comparisons were statistically significant on the primary and

key secondary endpoints. The two studies provided statistical evidence that ZX008 is superior to placebo in treating seizures associated with Dravet syndrome in patients 2 years and older.

2 INTRODUCTION

2.1 Overview

On September 25, 2019, Zogenix, Inc. (the Applicant) resubmitted an NDA for Fintelpa (fenfluramine, or ZX008 under the Applicant’s clinical program) for the treatment of seizures associated with Dravet syndrome in patients 2 years and older. The NDA resubmission contained two randomized, double-blind, placebo-controlled clinical studies to demonstrate the drug efficacy. The two clinical studies – Study 1 and Study ZX008-1504 Cohort 2 (hereafter referred to as Study 1504C2 in the review) – are summarized in the table below and reviewed in Section 3.

Table 2. Clinical studies in this review

Study Number	Design	Study Duration	Study Arm (Number of randomized subjects per arm)	Study Population
Study 1	Randomized, double-blind, placebo-controlled, parallel-group	6-week Baseline Period, 2-week Titration Period and 12-week Maintenance Period	0.8 mg/kg/day (40) 0.4 mg/kg/day (39) Placebo (40)	Male and female patients aged 2 to 18 years with Dravet syndrome
ZX008-1504 Cohort 2	Randomized, double-blind, placebo-controlled, parallel-group	6-week Baseline Period, 3-week Titration Period and 12-week Maintenance Period	0.5 mg/kg/day (43) Placebo (44)	Male and female patients aged 2 to 18 years with Dravet syndrome

Source: statistical reviewer’s summary

2.2 Data Sources

The electronic submission of this NDA resubmission is located at

<\\cdsesub1\evsprod\NDA212102\0011>

The study reports are located at

<\\cdsesub1\evsprod\NDA212102\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\seizures\5351-stud-rep-contr>

The datasets are located at

<\\cdsesub1\evsprod\NDA212102\0011\m5\datasets>
<\\cdsesub1\evsprod\NDA212102\0044\m5\datasets>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality and analysis quality were low. The original NDA was previously submitted on February 5, 2019 and issued a Refusal to File (RTF) letter on April 5, 2019 partly because the datasets for Study 1 were incorrect. The Applicant then conducted an independent quality assurance review of data for Study 1. The data issue identified in the RTF letter was resolved in the current resubmission, however, two other major data issues were found in the review of this resubmission.

The first data issue is that the inspection staffs discovered retrospective collections of the eDiary data during the conduct of both efficacy studies, which was neither pre-specified in the protocols nor disclosed in the NDA resubmission (see the Clinical Inspection Summary by Dr. Sheryl Grandinetti). During the review, several statistical/clinical information requests (IRs) were sent to the Applicant aiming to understand the nature and scope of the retrospective collections and evaluate their impact on efficacy evaluations. The quality of responses to the IRs was poor, as evident by the numbers of subsequent IRs and further corrected datasets needed to thoroughly address issues in the original IRs. Below the statistical reviewer provides an estimate of the extent to which the calculation of the daily convulsive seizure frequency was affected on a per patient per day basis:

- For Study 1, among the 16244 daily convulsive seizure frequencies from 119 randomized subjects used in the primary endpoint derivation in the initial NDA resubmission, 1390 (8.6%) daily convulsive seizure frequencies were different due to retrospective edit.
- For Study 1504C2, among the 12249 daily convulsive seizure frequencies from 87 randomized subjects used in the primary endpoint derivation in the initial NDA resubmission, 1129 (9.2%) daily convulsive seizure frequencies were different due to retrospective edit.

While the retrospective collections could reduce missing seizure diary data, some of the retrospective collections occurred long after the initial seizure record dates, casting doubt on the reliability of the retrospective collected data. For example, in Study 1 and Study 1504C2, some seizure counts were retrospective collected and edited more than 400 days after the initial seizure record dates. Due to the large amount of the retrospective collections, the Applicant was requested to submitted raw datasets that did not contain any retrospective edits, and the NDA resubmission was issued an extension of goal date by three months to provide time for a full review.

The second data issue is the derivation of the seizure frequency per 28 days during the Titration and Maintenance (T+M) periods. Study 1 protocol pre-specified that the end of study is Day 99 and has a window of ± 4 days; Study 1504C2 protocol pre-specified that the end of study is Day 106 and has a window of ± 4 days. However, in the actual derivation of the seizure frequency per 28 days during the T+M periods, days extended past the protocol-defined final days of the T+M

periods were included. For example, the derivation of the seizure frequency per 28 days during the T+M periods for one subject in Study 1 used seizure counts up to Day 131.

The statistical reviewer was able to perform independent review using the Applicant’s submitted datasets and confirm the Applicant’s analysis results in the resubmission and subsequent responses to IRs. In order to avoid introducing potential bias, the final datasets used to determine the efficacy do not include any retrospectively collected data or data extended past the protocol-defined final days of the T+M periods. In other words, data deviated from protocol/statistical analysis plan (SAP) pre-specifications were not used in the final efficacy determination. Analyses relying on datasets with retrospective collected data were also considered by the review teams. The results of these analyses did not show substantial numerical differences or different statistical conclusions (i.e. significances of the tests were not affected), compared to the efficacy analysis results in Section 3.2 of this review. Nonetheless, the impact of poor trial conduct on the efficacy evaluations remains difficult to evaluate.

3.2 Evaluation of Efficacy

3.2.1 Study 1

3.2.1.1 Design and Endpoints

Study 1 was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multi-center clinical study to evaluate the safety and efficacy of two doses of ZX008 in pediatric patients with Dravet syndrome. Approximately 105 subjects were planned to be randomized in a 1:1:1 ratio to the ZX008 0.8 mg/kg/day group, ZX008 0.2 mg/kg/day group, or placebo group. The randomization was stratified by age group (< 6 years, ≥ 6 years).

The study consisted of a 6-week Baseline Period, a 2-week Titration Period, a 12-week Maintenance Period, and an 8-day Taper Period. The titration algorithm during the Titration Period is summarized below.

Table 3. Study 1 titration algorithm

Randomized Group	Titration Step 1 Study Day 1-4	Titration Step 2 Study Days 5-8	Titration Step 3 Study Days 9-14
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.8 mg/kg/day
Placebo	Placebo	Placebo	Placebo

Note: maximum daily dose of ZX008 is 30 mg

Source: Table 3 in the protocol amendment 3.0

The primary efficacy endpoint was the change in the mean convulsive seizure frequency per 28 days between the Baseline and T+M periods.

The key secondary efficacy endpoints were

1. The proportion with ≥ 50% reduction from Baseline in convulsive seizure frequency
2. The longest interval between convulsive seizures (during the T+M periods)

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least one dose of ZX008 or placebo and for whom at least one week of diary data are available.

The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment, age group as factors and log-transformed baseline convulsive seizure frequency as the covariate. The response in the ANOCVA model was the log-transformation of convulsive seizure frequency per 28 days during the T+M periods plus 1, i.e., $\log(\text{convulsive seizure frequency} + 1)$.

The proportion with $\geq 50\%$ reduction from Baseline in convulsive seizure frequency was analyzed using a logistic regression model that included treatment and age group. The longest interval between convulsive seizures was analyzed by the Wilcoxon rank sum test. The Hodges-Lehmann estimates and 95% confidence intervals for the median longest interval between convulsive seizures were also planned. When comparing a ZX008 dose group and placebo group with respect to the proportion with $\geq 50\%$ reduction from Baseline in convulsive seizure frequency (or the longest interval between convulsive seizures), only data from the two groups in comparison were used in the logistic model (or Wilcoxon rank sum test).

The following testing hierarchy was pre-specified:

1. Comparison of ZX008 0.8 mg/kg/day and placebo on the primary endpoint
2. Comparison of ZX008 0.8 mg/kg/day and placebo on key secondary endpoint 1
3. Comparison of ZX008 0.8 mg/kg/day and placebo on key secondary endpoint 2
4. Comparison of ZX008 0.2 mg/kg/day and placebo on the primary endpoint
5. Comparison of ZX008 0.2 mg/kg/day and placebo on key secondary endpoint 1
6. Comparison of ZX008 0.2 mg/kg/day and placebo on key secondary endpoint 2

3.2.1.3 Subject Disposition, Demographic and Baseline Characteristics

A total of 173 subjects were enrolled in 47 study centers in 10 countries. A total of 119 subjects were randomized: 40 subjects (33.6%) were randomized to the ZX008 0.8 mg/kg/day group, 39 (32.8%) to the ZX008 0.2 mg/kg/day group, and 40 (33.6%) to the placebo group. Among the randomized subjects, a total of 117 subjects were included in the mITT population. One subject in the ZX008 0.2 mg/kg/day group and one subject in the placebo group were excluded from the mITT population because their Baseline convulsive seizure frequencies were missing or zero.

Table 4. Study 1 Subject demographics and baseline characteristics, mITT population

	Placebo (N=39)	ZX008 0.2 mg (N=38)	ZX008 0.8 mg (N=40)	Total (N=117)
Age (years)				
n	39	38	40	117
Mean	9.3	9.0	8.8	9.0
SD	5.15	4.56	4.41	4.68
Median	9.0	8.0	8.5	8.0
Min	2	2	2	2
Max	18	17	18	18
Age Group, n (%)				
<6 years	11 (28.2%)	9 (23.7%)	11 (27.5%)	31 (26.5%)
≥ 6 years	28 (71.8%)	29 (76.3%)	29 (72.5%)	86 (73.5%)
Sex				
Male	21 (53.8%)	21 (55.3%)	21 (52.5%)	63 (53.8%)
Female	18 (46.2%)	17 (44.7%)	19 (47.5%)	54 (46.2%)
Race				
White	30 (76.9%)	32 (84.2%)	34 (85.0%)	96 (82.1%)
Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	4 (10.3%)	2 (5.3%)	1 (2.5%)	7 (6.0%)
American Indian or Alaska Native	1 (2.6%)	1 (2.6%)	0 (0.0%)	2 (1.7%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (5.1%)	1 (2.6%)	1 (2.5%)	4 (3.4%)
Not Reported [*]	2 (5.1%)	2 (5.3%)	4 (10.0%)	8 (6.8%)
Unknown [*]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Height (m)				
n	39	38	40	117
Mean	1.28	1.31	1.28	1.29
SD	0.227	0.223	0.204	0.217
Median	1.28	1.33	1.30	1.30
Min	0.9	0.9	0.8	0.8
Max	1.8	1.8	1.7	1.8
Baseline Weight (kg)				
n	39	38	40	117
Mean	31.6	35.5	31.8	32.9
SD	16.34	19.71	13.47	16.60
Median	25.6	31.0	28.3	27.9
Min	14	13	12	12
Max	81	110	61	110
Baseline BMI (kg/m²)				
n	39	38	40	117
Mean	17.89	19.32	18.47	18.56
SD	3.821	5.688	3.502	4.423
Median	17.54	17.24	18.03	17.78
Min	11.6	13.5	12.5	11.6
Max	31.6	42.8	27.4	42.8

mITT = Modified intent-to-treat population, ROW = Rest of World.

*Not reported, or missing: Privacy laws in some regions/countries preclude disclosure of certain personal information.

BMI=Body Mass Index, where BMI = weight (kg) / height (m²).

Source: selected from Table 14.1.2.2_103d in the response to information request received on April 29, 2020

Table 4 summarizes the demographic and baseline characteristics of subjects in the mITT population. The treatment groups appeared similar in terms of age group, sex, race, and baseline height, weight, and body mass index. The average age of the subjects was approximately 9.0 years (standard deviation (SD) = 4.68). There were more males than females in the study. The majority of the subjects were white.

3.2.1.4 Results and Conclusions

Table 5. Study 1 analysis results of convulsive seizure frequency per 28 days, mITT population

	Placebo (N=39)	ZX008 0.2 mg (N=38)	ZX008 0.8 mg (N=40)
T + M PERIOD ANALYSIS			
Baseline Summary Statistics			
N	39	38	40
Mean (SD)	45.47 (40.691)	45.29 (101.054)	32.93 (32.332)
Median	29.44	18.14	18.67
Min, Max	(3.3, 148.2)	(2.7, 623.5)	(6.0, 124.0)
T+M Period Summary Statistics			
N	39	38	40
Mean (SD)	38.25 (36.959)	26.99 (38.729)	18.60 (32.497)
Median	24.57	11.64	3.74
Min, Max	(2.7, 163.7)	(0.0, 199.7)	(0.0, 169.9)
T+M Period: Parametric Model Summary[1]			
Results on log scale[1]			
Least Squares Mean (SE) [1]	3.04 (0.128)	2.68 (0.131)	1.94 (0.126)
95% CI for Least Squares Mean [1]	(2.79, 3.29)	(2.43, 2.94)	(1.70, 2.19)
Difference from Placebo:			
Estimate of A-P (95% CI)[1]		-0.36 (-0.70, -0.02)	-1.10 (-1.44, -0.76)
p-value for comparison with Placebo[2]		0.043	<0.001

mITT = Modified intent-to-treat population; CI = Confidence Interval; ANCOVA = Analysis of Covariance.
 Note: This sensitivity analysis summary excludes all seizure records that were entered via Data Clarification Form (DCF). Seizure records that were amended via DCF are included using the original values prior to the DCF. Seizures in the maintenance period recorded after study day 103 are excluded.
 [1] Baseline and T+M period values were log transformed prior to analysis. To avoid taking log of 0, a value of 1 was added to the T+M period values before log transformation.
 [2] Results are based on an ANCOVA model with treatment group (three levels) and age group (< 6 years, ≥ 6 years) as factors, log baseline convuls: seizure frequency as a covariate and log convulsive seizure frequency Titration + Maintenance period as response. The p-value is obtained from the ANCOVA model.

Source: selected from Table 14.2.1.2_103d in the response to information request received on March 31, 2020

Table 5 presents the analysis results of convulsive seizure frequency per 28 days. The summary statistics in the table were calculated for the raw (i.e. not log-transformed) baseline convulsive seizure frequency per 28 days and raw T+M period convulsive seizure frequency per 28 days. The raw baseline convulsive seizure frequency appeared different across treatment groups, which is probably caused by the large variability among subjects and skewness of the data within each treatment group. The log-transformed convulsive seizure frequencies were less skewed and had smaller variability. As described in Section 3.2.1.2, the primary analysis model used the log-transformed convulsive seizure frequency plus 1 as the response. Compared to the placebo group, both ZX008 groups had less seizures on average during the T+M periods. The comparison between the ZX008 0.8 mg/kg/day group and placebo group on the primary endpoint was statistically significant (p-value < 0.001). Since the comparisons between the ZX008 0.8 mg/kg/day group and placebo group on the two key secondary endpoints also had p-values smaller than 0.05 (see more details in **Table 6**), the comparison between the ZX008 0.2 mg/kg/day group and placebo group on the primary endpoint is considered statistically significant (p-value = 0.043).

Based on the least squares means from the primary analysis results, the percentage difference relative to placebo can be derived using the following formula:

$$\frac{[\exp(LS\text{Mean}(\text{drug}))-1]-[\exp(LS\text{Mean}(\text{placebo}))-1]}{\exp(LS\text{Mean}(\text{placebo}))-1} \times 100\%$$

Therefore, the percentages of difference relative to placebo were -31.7% and -70.0% for the ZX008 0.2 mg/kg/day group and ZX008 0.8 mg/kg/day group, respectively.

Table 6. Study 1 analysis results of key secondary endpoints, mITT population

	Statistic	mITT: Parametric Analysis		
		Placebo	0.2 mg/kg/ day	0.8 mg/kg/ day
≥ 50% Reduction Responder	N	39	38	40
	Number of Subjects Experienced	3	13	28
	Percent of Subjects Experienced	7.7%	34.2%	70.0%
	p-value		0.007	<0.001
Median Longest Interval Between Convulsive Seizures (SEIZLNG1)	N	39	38	40
	Median (days)	9.0	16.50	21.50
	p-value		0.029	<0.001
Median Longest Interval Between Convulsive Seizures (SEIZLNG2)	N	39	38	40
	Median (days)	8.0	13.0	20.50
	p-value		0.043	<0.001

Source: Table B in the response to information request received on March 31, 2020

Table 6 presents the analysis results of the two key secondary endpoints. The percentages of responders were 7.7%, 34.2%, and 70.0% for the placebo group, ZX008 0.2 mg/kg/day group, and ZX008 0.8 mg/kg/day group, respectively. Both the ZX008 0.8 mg/kg/day group and the ZX008 0.2 mg/kg/day group were statistically better than the placebo (p-value < 0.001 and p-value = 0.007, respectively).

In terms of handling missing data when deriving the longest interval between convulsive seizures, if a subject has two consecutive days with missing diary data, the SAP pre-specified that the current interval without seizures “will be ended on the first date of missing diary data, and a new one begun on the next date that diary data are available and no seizure occurs.” The SAP did not pre-specify how a missing diary day will be treated if the two adjacent days of the missing day had diary data. In the initial analysis results submitted by the Applicant, such missing diary days were imputed as days without seizures. Based on data using this imputation approach, the median longest interval between convulsive seizures were 9.0 days, 16.5 days, and 21.5 days for the placebo group, ZX008 0.2 mg/kg/day group, and ZX008 0.8 mg/kg/day group, respectively. Both the ZX008 0.8 mg/kg/day group and the ZX008 0.2 mg/kg/day group were statistically better than the placebo (p-value < 0.001 and p-value = 0.029, respectively).

The Applicant was also requested to derive the longest interval between convulsive seizures assuming that on all day of missing diary data, the subjects experienced convulsive seizures. With this more conservative missing data imputation, the comparisons between the ZX008 groups and placebo group were also statistically significant (p-value < 0.001 for the comparison between ZX008 0.8 mg/kg/day group and placebo group; p-value = 0.043 for the comparison between ZX008 0.2 mg/kg/day group and placebo group). The median longest interval between convulsive

seizures were 8.0 days, 13.0 days, and 20.5 days for the placebo group, ZX008 0.2 mg/kg/day group, and ZX008 0.8 mg/kg/day group, respectively.

3.2.2 Study 1504C2

3.2.2.1 Design and Endpoints

Study 1504C2 was the second cohort of Study ZX008-1504, the first cohort of which was to assess the pharmacokinetic and safety profile of ZX008 when added to standard of care. Study 1504C2 was a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multi-center clinical study to evaluate the safety and efficacy of ZX008 in pediatric patients with Dravet syndrome. Approximately 70 subjects were planned to be randomized in a 1:1 ratio to the ZX008 0.5 mg/kg/day group or placebo group. The randomization was stratified by age group (< 6 years, ≥ 6 years).

The study consisted of a 6-week Baseline Period, a 3-week Titration Period, a 12-week Maintenance Period, and a 2-week Taper Period. The titration algorithm during the Titration Period is summarized below.

Table 7. Study 1504C2 titration algorithm

Randomized Dose	Titration Step 1 Study Days 1-7	Titration Step 2 Study Days 8-14	Titration Step 3 Study Days 15-21
ZX008 0.5 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.5 mg/kg/day
Placebo	Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 20 mg; the dosing regimen for all doses is BID			

Source: Table 5 in the protocol amendment 3.1

The primary efficacy endpoint was the change in the mean convulsive seizure frequency per 28 days between the Baseline and Titration and Maintenance (T+M) periods.

The key secondary efficacy endpoints were

1. The proportion with ≥ 50% reduction from Baseline in convulsive seizure frequency
2. The longest interval between convulsive seizures (during the T+M periods)

3.2.2.2 Statistical Methodologies

The efficacy analysis population was the modified intention-to-treat (mITT) population, defined as all randomized subjects who receive at least one dose of ZX008 or placebo and for whom at least one week of diary data are available.

The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment, age group as factors and log-transformed baseline convulsive seizure frequency as the

covariate. The response in the ANOCVA model was the log-transformed convulsive seizure frequency per 28 days during the T+M periods.

The proportion with $\geq 50\%$ reduction from Baseline in convulsive seizure frequency was analyzed using a logistic regression model that included treatment and age group. The longest interval between convulsive seizures was analyzed by the Wilcoxon rank sum test. The Hodges-Lehmann estimate and 95% confidence interval for the median longest interval between convulsive seizures were also planned.

The following testing hierarchy was pre-specified:

1. Comparison of ZX008 0.5 mg/kg/day and placebo on the primary endpoint
2. Comparison of ZX008 0.5 mg/kg/day and placebo on key secondary endpoint 1
3. Comparison of ZX008 0.5 mg/kg/day and placebo on key secondary endpoint 2

3.2.2.3 Subject Disposition, Demographic and Baseline Characteristics

A total of 115 subjects were enrolled in 28 study centers in 7 countries. A total of 87 subjects were randomized: 44 subjects (50.6%) were randomized to the ZX008 0.5 mg/kg/day group and 43 (49.4%) to the placebo group. Among the randomized subjects, a total of 85 subjects were included in the mITT population. Two subjects in the ZX008 0.5 mg/kg/day group were excluded from the mITT population because the Baseline convulsive seizure frequencies were missing or zero.

Table 8. Study 1504C2 Subject demographics and baseline characteristics, mITT population

	Placebo (N=42)	ZX008 0.5 mg (N=43)	Total (N=85)
Age (years)			
n	42	43	85
Mean	9.3	8.8	9.0
SD	5.06	4.56	4.79
Median	9.0	9.0	9.0
Min	2	2	2
Max	19	18	19
Age Group, n (%)			
<6 Years	12 (28.6%)	12 (27.9%)	24 (28.2%)
>=6 Years	30 (71.4%)	31 (72.1%)	61 (71.8%)
Sex			
Male	26 (61.9%)	23 (53.5%)	49 (57.6%)
Female	16 (38.1%)	20 (46.5%)	36 (42.4%)
Race			
White	28 (66.7%)	23 (53.5%)	51 (60.0%)
Black or African American	1 (2.4%)	1 (2.3%)	2 (2.4%)
Asian	1 (2.4%)	2 (4.7%)	3 (3.5%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (2.4%)	3 (7.0%)	4 (4.7%)
Not Reported [*]	11 (26.2%)	13 (30.2%)	24 (28.2%)
Unknown [*]	0 (0.0%)	1 (2.3%)	1 (1.2%)
Baseline Height (m)			
n	42	43	85
Mean	1.30	1.31	1.31
SD	0.239	0.235	0.236
Median	1.33	1.32	1.32
Min	0.9	0.8	0.8
Max	1.8	1.8	1.8
Baseline Weight (kg)			
n	42	43	85
Mean	35.3	31.3	33.3
SD	19.95	14.85	17.57
Median	30.5	27.9	28.6
Min	13	13	13
Max	90	75	90
Baseline BMI (kg/m²)			
n	42	43	85
Mean	19.17	17.32	18.23
SD	4.923	2.715	4.047
Median	17.51	16.58	17.13
Min	13.2	13.7	13.2
Max	35.0	24.1	35.0

*Not reported, or missing: Privacy laws in some regions/countries preclude disclosure of certain personal information.
 BMI=Body Mass Index, where BMI = weight (kg) / height² (m²).

Source: selected from Table 14.1.2.2b_110d in the response to information request received on April 29, 2020

Table 8 summarizes the demographic and baseline characteristics of subjects in the mITT population. The treatment groups appeared similar in terms of age group, sex, race, and baseline height, weight, and body mass index. The average age of the subjects was approximately 9.0 years (SD = 4.79). There were more males than females in the study. The majority of the subjects were white.

3.2.2.4 Results and Conclusions

Table 9. Study 1504C2 analysis results of convulsive seizure frequency per 28 days, mITT population

	Placebo (N=42)	ZX008 0.5 mg (N=43)
T + M PERIOD ANALYSIS		
Baseline Summary Statistics		
N	42	43
Mean (SD)	23.22 (28.818)	29.34 (37.963)
Median	11.48	15.02
Min, Max	(0.7, 162.7)	(2.0, 213.3)
T+M Period Summary Statistics		
N	42	43
Mean (SD)	22.34 (28.399)	26.88 (74.497)
Median	11.71	5.03
Min, Max	(2.4, 170.1)	(0.0, 469.0)
T+M Period: Parametric Model Summary[1]		
Results on log scale[1]		
Least Squares Mean (SE) [1]	2.77 (0.147)	1.96 (0.144)
95% CI for Least Squares Mean [1]	(2.48, 3.06)	(1.67, 2.24)
Difference from Placebo:		
Estimate of A-P (95% CI)[1]		-0.82 (-1.19, -0.44)
p-value for comparison with Placebo[2]		<0.001

mITT = Modified intent-to-treat population; CI = Confidence Interval; ANCOVA = Analysis of Covariance.
 Note: This sensitivity analysis summary excludes all seizure records that were entered via Data Clarification Form (DCF). Seizure records that were amended via DCF are included using the original values prior to the DCF. Seizures in the maintenance period recorded after study day 110 are excluded.
 [1] Baseline and T+M period values were log transformed prior to analysis. To avoid taking log of 0, a value of 1 was added to the T+M period value before log transformation.
 [2] Results are based on an ANCOVA model with treatment group and age group (< 6 years, ≥ 6 years) as factors, log baseline convulsive seizure frequency per 28 days as a covariate and log convulsive seizure frequency per 28 days during T+M period as response. The p-value is obtained from this ANCOVA model.

Source: selected from Table 14.2.1.2b_110d in the response to information request received on March 31, 2020

Table 9 presents the analysis results of convulsive seizure frequency per 28 days. The summary statistics in the table were calculated for the raw (i.e. not log-transformed) baseline convulsive seizure frequency per 28 days and raw T+M period convulsive seizure frequency per 28 days. The primary analysis model used the log-transformed convulsive seizure frequency plus 1 as the response. The SAP pre-specified that the log-transformed convulsive seizure frequency (i.e. without adding 1 to it before log transformation) is the response in the primary analysis model. The added value of 1 does not change the statistical conclusion of the comparison between the ZX008 0.5 mg/kg/day group and placebo group on the primary endpoint; the ZX008-placebo comparison was statistically significant (p-value < 0.001, with or without adding 1 to the convulsive seizure frequency before log transformation). The percentages of difference relative to placebo was -59.5% for the ZX008 group.

Table 10. Study 1504C2 analysis results of key secondary endpoints, mITT population

	Statistic	Placebo	0.5 mg/ kg/day
≥ 50% Reduction Responder	N	42	43
	Number of Subjects Experienced	2	23
	Percent of Subjects Experienced	4.8%	53.5%
	p-value		<0.001
Median Longest Interval Between Convulsive Seizures	N	42	43
	Median (days)	13.0	22.0
	p-value		0.011
Median Longest Interval Between Convulsive Seizures (SEIZLNGI2)	N	42	43
	Median (days)	12.0	17.0
	p-value		0.010

Source: Table D in the response to information request received on March 31, 2020

Table 10 presents the analysis results of the two key secondary endpoints. The percentages of responders were 4.8% and 53.5% for the placebo group and ZX008 0.5 mg/kg/day group, respectively. The ZX008 group was statistically better than the placebo group (p-value < 0.001).

Regarding the results for the longest interval between convulsive seizures, see a detailed description of calculations of this endpoint under two different imputation methods in Section 3.2.1.4. When missing diary days whose adjacent days did not miss diary data were treated as days without convulsive seizures, the median longest interval between convulsive seizures were 13.0 days and 22.0 days for the placebo group and ZX008 0.5 mg/kg/day group, respectively. The ZX008 group was statistically better than the placebo group (p-value < 0.011).

When all missing diary days were treated as days that the subjects experienced convulsive seizures, the median longest interval between convulsive seizures were 12.0 days and 17.0 days for the placebo group and ZX008 0.8 mg/kg/day group, respectively. The ZX008 and placebo comparison remained statistically significant (p-value = 0.010).

3.3 Evaluation of Safety

Please refer to Dr. Natalie Getzoff's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 1

4.1.1 Gender, Race, Age, and Geographic Region

Table 11. Study 1 analyses of convulsive seizure frequency per 28 days by sex, mITT population

Convulsive seizure frequency per 28 days	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
Female			
n	18	17	19
Baseline mean (SD)	43.05 (37.80)	58.30 (147.63)	35.13 (32.59)
T+M period LS mean (SD) (on log scale)	2.94 (0.16)	2.54 (0.17)	1.81 (0.16)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.40 (-0.85, 0.05)	-1.13 (-1.57, -0.69)
Male			
n	21	21	21
Baseline mean (SD)	47.54 (43.83)	34.75 (34.57)	30.94 (32.77)
T+M period LS mean (SD) (on log scale)	3.14 (0.20)	2.82 (0.20)	2.07 (0.19)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.33 (-0.85, 0.19)	-1.08 (-1.60, -0.56)

Source: selected from Table 14.2.1.2_103d_sex in the response to information request received on April 29, 2020

Table 12. Study 1 analyses of convulsive seizure frequency per 28 days by race, mITT population

Convulsive seizure frequency per 28 days	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
Non-White*			
n	9	6	6
Baseline mean (SD)	33.18 (37.29)	25.44 (25.62)	12.35 (7.17)
T+M period LS mean (SD) (on log scale)	2.63 (0.32)	2.38 (0.45)	1.29 (0.39)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.25 (-1.24, 0.74)	-1.33 (-2.30, -0.36)
White			
n	30	32	34
Baseline mean (SD)	49.15 (41.53)	49.01 (109.51)	36.56 (33.72)
T+M period LS mean (SD) (on log scale)	3.15 (0.14)	2.77 (0.14)	2.07 (0.13)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.39 (-0.76, -0.01)	-1.08 (-1.45, -0.72)

*Including subjects whose races were missing

Source: selected from Table 14.2.1.2_103d_race in the response to information request received on April 29, 2020

Table 13. Study 1 analyses of convulsive seizure frequency per 28 days by region, mITT population

Convulsive seizure frequency per 28 days	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
Non-US			
n	16	15	17
Baseline mean (SD)	39.21 (37.73)	23.46 (24.99)	23.96 (26.58)
T+M period LS mean (SD) (on log scale)	2.73 (0.21)	1.95 (0.21)	1.48 (0.20)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.78 (-1.33, -0.23)	-1.25 (-1.78, -0.72)
US			
n	23	23	23
Baseline mean (SD)	49.82 (42.90)	59.82 (127.44)	39.56 (35.09)
T+M period LS mean (SD) (on log scale)	3.24 (0.16)	3.14 (0.16)	2.23 (0.16)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.10 (-0.52, 0.32)	-1.01 (-1.43, -0.58)

Source: selected from Table 14.2.1.2_103d_region in the response to information request received on April 29, 2020

Table 11, **Table 12**, and **Table 13** present the analyses of the primary endpoint by sex, race, and geographic region, respectively. There is no compelling evidence from these subgroup analyses that a specific sex, race, or geographic region benefits differently from ZX008.

Table 14. Study 1 analyses of key secondary endpoints by sex, mITT population

	Statistic	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
≥ 50% reduction from Baseline in convulsive seizure frequency				
Female	n	18	17	19
	Number of subjects experienced (%)	1 (5.6)	7 (41.2)	15 (78.9)
Male	n	21	21	21
	Number of subjects experienced (%)	2 (9.5)	6 (28.6)	13 (61.9)
Longest interval between convulsive seizures[†]				
Female	n	18	17	19
	Mean (SD)	9.8 (6.6)	19.9 (22.9)	27.7 (23.3)
	Median	8.5	13.0	17.0
Male	n	21	21	21
	Mean (SD)	9.4 (5.9)	16.1 (20.8)	32.2 (29.2)
	Median	7.0	13.0	21.0

[†] Days missing dairy data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1_103d_sex and Table 14.2.3.1.2_103d_sex in the response to information request received on April 29, 2020

Table 15. Study 1 analyses of key secondary endpoints by race, mITT population

	Statistic	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
≥ 50% reduction from Baseline in convulsive seizure frequency				
Non-White*	n	9	6	6
	Number of subjects experienced (%)	1 (11.1)	2 (33.3)	5 (83.3)
White	n	30	32	34
	Number of subjects experienced (%)	2 (6.7)	11 (34.4)	23 (67.6)
Longest interval between convulsive seizures[†]				
Non-White*	n	9	6	6
	Mean (SD)	9.9 (7.2)	10.7 (5.1)	37.8 (26.1)
	Median	7.0	9.5	34.5
White	n	30	32	34
	Mean (SD)	9.5 (6.0)	19.2 (23.2)	28.7 (26.5)
	Median	8.0	13.0	20.0

* Including subjects whose races were missing

[†] Days missing dairy data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1_103d_race and Table 14.2.3.1.2_103d_race in the response to information request received on April 29, 2020

Table 16. Study 1 analyses of key secondary endpoints by region, mITT population

	Statistic	Placebo (N = 39)	ZX008 0.2 mg/kg/day (N = 38)	ZX008 0.8 mg/kg/day (N = 40)
≥ 50% reduction from Baseline in convulsive seizure frequency				
Non-US	n	16	15	17
	Number of subjects experienced (%)	2 (12.5)	7 (46.7)	13 (76.5)
US	n	23	23	23
	Number of subjects experienced (%)	1 (4.3)	6 (26.1)	15 (65.2)
Longest interval between convulsive seizures[†]				
Non-US	n	16	15	17
	Mean (SD)	10.2 (6.3)	28.5 (31.0)	37.0 (27.6)
	Median	8.0	16.0	29.0
US	n	23	23	23
	Mean (SD)	9.1 (6.2)	10.9 (6.4)	25.0 (24.7)
	Median	7.0	9.0	14.0

[†] Days missing diary data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1_103d_region and Table 14.2.3.1.2_103d_region in the response to information request received on April 29, 2020

Table 14, Table 15, and Table 16 present the analyses of the key secondary endpoints by sex, race, and geographic region, respectively. There is no compelling evidence from these subgroup analyses that a specific sex, race, or geographic region benefits differently from ZX008.

4.1.2 Other Subgroup Populations

Please refer to Dr. Natalie Getzoff's clinical review for analyses of other subgroups.

4.2 Study 1504C2

4.2.1 Gender, Race, Age, and Geographic Region

Table 17. Study 1504C2 analyses of convulsive seizure frequency per 28 days by sex, mITT population

	Placebo (N = 42)	ZX008 0.8 mg/kg/day (N = 43)
Female		
n	16	20
Baseline mean (SD)	26.89 (19.49)	33.19 (48.77)
T+M period LS mean (SD) (on log scale)	2.84 (0.26)	2.10 (0.23)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.74 (-1.38, -0.11)
Male		
n	26	23
Baseline mean (SD)	20.96 (33.47)	25.99 (25.93)
T+M period LS mean (SD) (on log scale)	2.71 (0.17)	1.92 (0.18)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.80 (-1.26, -0.33)

Source: selected from Table 14.2.1.2b_110d_sex in the response to information request received on April 29, 2020

Table 18. Study 1504C2 analyses of convulsive seizure frequency per 28 days by race, mITT population

	Placebo (N = 42)	ZX008 0.8 mg/kg/day (N = 43)
Non-White*		
n	14	20
Baseline mean (SD)	18.83 (18.19)	18.87 (23.79)
T+M period LS mean (SD) (on log scale)	2.65 (0.24)	1.36 (0.20)
LS mean difference from placebo (95% CI) (on log scale)	--	-1.29 (-1.87, -0.71)
White		
n	28	23
Baseline mean (SD)	24.42 (32.97)	38.44 (45.57)
T+M period LS mean (SD) (on log scale)	2.91 (0.19)	2.45 (0.20)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.46 (-0.96, 0.04)

* Including subjects whose races were missing

Source: selected from Table 14.2.1.2b_110d_race in the response to information request received on April 29, 2020

Table 19. Study 1504C2 analyses of convulsive seizure frequency per 28 days by region, mITT population

	Placebo (N = 42)	ZX008 0.8 mg/kg/day (N = 43)
Non-US		
n	32	32
Baseline mean (SD)	23.94 (31.73)	20.31 (21.76)
T+M period LS mean (SD) (on log scale)	2.62 (0.15)	1.64 (0.15)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.98 (-1.37, -0.59)
US		
n	10	11
Baseline mean (SD)	20.92 (17.53)	55.63 (59.70)
T+M period LS mean (SD) (on log scale)	3.59 (0.43)	3.05 (0.36)
LS mean difference from placebo (95% CI) (on log scale)	--	-0.54 (-1.48, 0.40)

Source: selected from Table 14.2.1.2b_110d_region in the response to information request received on April 29, 2020

Table 17, Table 18, and Table 19 present the analyses of the primary endpoint by sex, race, and geographic region, respectively. There is no compelling evidence from these subgroup analyses that a specific sex, race, or geographic region benefits differently from ZX008.

Table 20. Study 1504C2 analyses of key secondary endpoints by sex, mITT population

	Statistic	Placebo (N = 42)	ZX008 0.5 mg/kg/day (N = 43)
≥ 50% reduction from Baseline in convulsive seizure frequency			
Female	n	16	20
	Number of subjects experienced (%)	1 (6.3)	12 (60.0)
Male	n	26	23
	Number of subjects experienced (%)	1 (3.8)	11 (47.8)
Longest interval between convulsive seizures[†]			
Female	n	16	20
	Mean (SD)	11.8 (5.0)	26.9 (22.6)
	Median	12.0	19.5
Male	n	26	23
	Mean (SD)	12.6 (7.4)	28.9 (30.1)
	Median	11.5	17.0

[†] Days missing dairy data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1.1b_110d_sex and Table 14.2.3.1.2b_110d_sex in the response to information request received on April 29, 2020

Table 21. Study 1504C2 analyses of key secondary endpoints by race, mITT population

	Statistic	Placebo (N = 42)	ZX008 0.5 mg/kg/day (N = 43)
≥ 50% reduction from Baseline in convulsive seizure frequency			
Non-White*	n	14	20
	Number of subjects experienced (%)	0 (0.0)	12 (60.0)
White	n	28	23
	Number of subjects experienced (%)	2 (7.1)	11 (47.8)
Longest interval between convulsive seizures[†]			
Non-White*	n	14	20
	Mean (SD)	11.3 (4.5)	38.3 (27.5)
	Median	10.5	29.5
White	n	28	23
	Mean (SD)	12.8 (7.4)	18.9 (22.7)
	Median	12.5	12.0

* Including subjects whose races were missing

[†] Days missing dairy data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1.1b_110d_race and Table 14.2.3.1.2b_110d_race in the response to information request received on April 29, 2020

Table 22. Study 1504C2 analyses of key secondary endpoints by region, mITT population

	Statistic	Placebo (N = 42)	ZX008 0.5 mg/kg/day (N = 43)
≥ 50% reduction from Baseline in convulsive seizure frequency			
Non-US	n	32	32
	Number of subjects experienced (%)	2 (6.3)	19 (59.4)
US	n	10	11
	Number of subjects experienced (%)	0 (0.0)	4 (36.4)
Longest interval between convulsive seizures[†]			
Non-US	n	32	32
	Mean (SD)	12.1 (5.1)	31.6 (28.6)
	Median	12.0	22.5
US	n	10	11
	Mean (SD)	12.8 (10.3)	17.4 (16.2)
	Median	9.5	12.0

[†] Days missing dairy data were imputed as days with convulsive seizures.

Source: selected from Table 14.2.2.1.1b_110d_region and Table 14.2.3.1.2b_110d_region in the response to information request received on April 29, 2020

Table 20, Table 21, and Table 22 present the analyses of the key secondary endpoints by sex, race, and geographic region, respectively. There is no compelling evidence from these subgroup analyses that a specific sex, race, or geographic region benefits differently from ZX008, except that a benefit from ZX008 in terms of median longest interval between convulsive seizures was not observed in US subjects.

4.2.2 Other Subgroup Populations

Please refer to Dr. Natalie Getzoff's clinical review for analyses of other subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The statistical issues were described in detail in Section 3.1 of this review. The impact of poor data and analysis quality on the efficacy evaluations was investigated. The concern over the impact of the retrospective edits and deviations from protocol/SAP pre-specifications on the efficacy conclusions was addressed in the responses to information requests during the review of the NDA resubmission. Data deviated from protocol/SAP pre-specifications were not used in the final efficacy determination in order to avoid introducing bias to the efficacy evaluations. The impact of poor trial conduct on the efficacy evaluations remains difficult to evaluate.

5.2 Collective Evidence

In Both Study 1 and Study 1504C2, the ZX008-placebo comparisons were statistically significant on the primary and key secondary endpoints. The two studies provided statistical evidence that ZX008 is superior to placebo in treating seizures associated with Dravet syndrome in patients 2 years and older.

5.3 Conclusions and Recommendations

From a statistical standpoint, based on evidence from Study 1 and Study 1504 Cohort 2, Fintepla (fenfluramine) is effective in treating seizures associated with Dravet syndrome in patients 2 years and older. However, a comprehensive evaluation of benefit-risk is still needed for the final determination to approve this NDA or not.

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/s/

XIANGMIN ZHANG
06/11/2020 10:40:01 AM

KUN JIN
06/11/2020 02:14:10 PM
I concur with the review.

HSIEN MING J HUNG
06/11/2020 02:53:01 PM