CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212102Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	212102
Priority or Standard	Priority
Submit Date(s)	2/5/2019 (original) 9/25/2019 (resubmission after refuse-to-file)
Received Date(s)	2/5/2019 (original) 9/25/2019 (resubmission after refuse-to-file)
PDUFA Goal Date	3/25/2020, extension to 6/25/2020 after Major Amendment
Division/Office	DN2/ON
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	6/25/2020
Established/Proper Name	Fenfluramine
(Proposed) Trade Name	Fintepla
Applicant	Zogenix, Inc
Dosage Form(s)	Oral solution (2.2 mg/mL)
Applicant Proposed Dosing Regimen(s)	0.2-0.7 mg/kg/day, maximum 26 mg/day, in patients not taking concomitant stiripentol; maximum 0.4 mg/kg/day or 17 mg/day in patients taking concomitant stiripentol. All doses are divided BID.
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBD	cannabidiol
CBZ	carbamazepine
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLB	clobazam
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DEE	developmental and/or epileptic encephalopathy
DMC	data monitoring committee
DS	Dravet syndrome
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
GTC	generalized tonic clonic
ICH	International Council for Harmonization
IDSMC	Independent Data Safety Monitoring Committee
IND	Investigational New Drug Application
INR	international normalized ratio

IPCAB	International Pediatric Cardiology Advisory Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	Interactive voice response system
LEV	levetiracetam
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
nCLB	norclobazam
NDA	new drug application
norFEN	norfenfluramine
NME	new molecular entity
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial onset seizure(s)
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PV	pharmacovigilance
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy patients
TEAE	treatment emergent adverse event
TPM	topiramate
VPA	valproic acid or valproate

Primary FDA text, ***reviewer comments***, *extracted from Applicant documents, extracted from other discipline reviews or FDA documents*

1. Executive Summary

1.1. Product Introduction

The Applicant is planning to market fenfluramine (proposed proprietary name Fintepla, investigational name ZX008) in the United States (U.S.). Fenfluramine (FEN) is an amphetamine analogue that increases the extracellular levels of 5-hydroxytryptamine (5-HT, serotonin) in nervous tissue. Although the mechanism of action remains unclear and may depend on multiple factors, it is theorized that fenfluramine reduces seizures by increasing extrasynaptic serotonin levels through modulation of serotonin receptors (primarily 5-HT_{1A} receptors); however, there is some evidence that the fenfluramine molecule (and possibly its metabolites) reduce seizures by binding at specific receptors, including 5-HT_{2A} and 5-HT_{2B} receptors.

Fenfluramine was originally approved in the U.S. in 1973 as Pondimin® (20 mg tablets) and Ponderex® (20 mg capsules) for use as an anorectic agent and was prescribed both alone and in combination with phentermine ("fen-phen") as an appetite suppressant for the treatment of adult obesity. It was withdrawn from the worldwide market in in the late 1990's (1997 in the U.S.) due to drug-related left-sided cardiac valvular disease.[1,2] On March 8, 1999, fenfluramine and dexfenfluramine were included in a Federal Register notice identifying drug products that were withdrawn from the U.S. market due to reasons of safety or effectiveness.[3] In 2015, the FDA determined that Pondimin® and Ponderex® specifically were withdrawn from the U.S. market due to reasons of safety or effectiveness.[4]

Fenfluramine is highly soluble in water; thus, the intended formulation is an aqueous solution. Sucralose (a sweetener) and cherry flavor were added to increase palatability and hydroxy-ethylcellulose as a thickener. The Applicant proposes to market an oral solution of 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.

The Applicant's proposed indication for FEN (Fintepla) is "Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older".

The Applicant proposes initiation of dosing at 0.2 mg/kg/day and increased to 0.4 mg/kg/day on

[1] Connolly HM, et al. Valvular heart disease associated with fenfluramine-phentermine. NEJM 1997 Aug 28;337(9): 581-8.
[2] CDC Morbidity and Mortality Weekly Report, 14 Nov 1997; 46(45): 1061-6.
[3] https://www.govinfo.gov/content/pkg/FR-1999-03-08/pdf/99-5517.pdf
[4] https://www.federalregister.gov/documents/2015/09/29/2015-24619/determination-that-pondimin-fenfluramine-hydrochloride-tablets-20-milligrams-and-60-milligrams-and

day 7 and 0.7 mg/kg/day (maximum) on day 14 in patients who are not on concomitant stiripentol (STP). For patients taking concomitant STP, the starting dose is 0.2 mg/kg/day with an increase to 0.4 mg/kg/day. The maximum daily dose is 26 mg for patients not on STP and 17 mg for those on concomitant STP. These doses are comparable to the dosing of the 2.5 mg/mL oral solution of the hydrochloride salt used in the clinical trials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval. The Applicant provided data from two adequate and well controlled studies that demonstrated that fenfluramine, as compared to placebo, reduces the frequency of convulsive seizures in patients with Dravet. The Applicant showed this effect for three doses (0.2 and 0.8 mg/kg/day in the absence of concomitant stiripentol and 0.5 mg/kg/day in patients taking concomitant stiripentol). The primary endpoint was statistically significant for all three doses in the two trials. Key secondary endpoints were statistically significant consistently in both trials. The treatment effect observed in these trials was comparable to what has been accepted in other FDA approved drugs for Dravet syndrome.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Fenfluramine, an amphetamine analogue that modulates serotonin receptors, was previously approved in the United States (U.S.) as an anorectic agent under the name Pondimin®. It was withdrawn from the U.S. market in 1997 due to drug-related valvular heart disease and pulmonary arterial hypertension and was determined to have been withdrawn from the U.S. market due to safety in 2015. It is now proposed for the treatment of seizures in patients with Dravet syndrome. Fenfluramine is an oral solution given twice daily by mouth.

Dravet syndrome is a severe epilepsy syndrome that presents as early as 6 months of age with multiple seizure types and cognitive impairment/developmental delay due at least in part to the seizures. The seizures are frequent and often refractory to multiple medications and other treatments. Patients with Dravet syndrome have increased risk of prolonged seizures (and status epilepticus) and higher mortality (~15%) compared to the general pediatric population with epilepsy. Rates of sudden unexplained death in epilepsy (SUDEP) are notably greater in the Dravet population than in the epilepsy population at large. Patients with Dravet syndrome are almost always significantly disabled by the seizures and cognitive impairment. There are two approved seizure treatments for patients with Dravet syndrome (cannabidiol and stiripentol), which are moderately effective and have significant adverse effects. The data from one of the fenfluramine clinical trials suggests that fenfluramine may be more efficacious than stiripentol.

The efficacy of fenfluramine was demonstrated in two randomized clinical trials, in which fenfluramine + standard of care was compared to standard of care treatment alone. There is evidence of clinical benefit based on reduction of monthly convulsive seizure frequency. Key secondary outcome measures were supportive.

Fenfluramine at 0.2 and 0.8 mg/kg/day without concomitant stiripentol and 0.5 mg/kg/day with concomitant stiripentol demonstrated reduction in convulsive seizures from baseline as compared to placebo. Patients taking 0.2 and 0.8 mg/kg/day had 32% and 70% reductions in mean convulsive seizure frequency compared to placebo. Patients taking 0.5 mg/kg/day + stiripentol had a 60% reduction in mean convulsive seizure frequency compared to placebo + stiripentol. Additionally, a greater proportion of patients in the fenfluramine groups were considered responders (50% reduction in seizure frequency) and patients in the fenfluramine groups had longer intervals between convulsive seizures during the treatment periods.

Risks identified in the clinical safety data include decreased appetite, decreased weight, and weight loss; and somnolence, sedation, and lethargy. Somnolence is observable and decreased appetite with weight loss may be observed and measured. When necessary, an intervention of fenfluramine dose reduction or discontinuation can take place.

The most concerning risks associated with fenfluramine are valvular heart disease (particularly aortic and/or mitral regurgitation) and

pulmonary arterial hypertension, neither of which were observed in the current development program. These fenfluramine-related adverse effects were reported in the 1990's and considered to be due to fenfluramine and the closely-related drug dexfenfluramine, based on case report studies, meta-analyses, and retrospective reports. Duration of treatment of fenfluramine appears to be a risk factor for development of either valvular heart disease or pulmonary hypertension, and magnitude of the dose may also play a role. Some patients who developed these disorders were symptomatic, and some required lifelong treatment and/or surgery. The risk of developing valvular heart disease or pulmonary hypertension cannot be completely prevented. However, the risk can be mitigated with regular monitoring of cardiac valvular structure and function and of estimated pulmonary arterial pressures via echocardiography. A Risk Evaluation and Mitigation Strategy (REMS) has been developed to moderate these risks.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dravet syndrome is a severe form of childhood epilepsy characterized by early onset of refractory seizures of multiple types, frequent episodes of status epilepticus, and developmental arrest or regression. Patients typically present prior to 2 years of age with a variety of disabling seizure types and developmental delay. The cognitive impairment is considered to be, at least in part, caused by the seizures. Although the diagnosis of DS is made by clinical criteria, most (80%) of patients with DS have mutations in the SCN1A gene, but the individual mutations vary widely. • Seizures in patients with Dravet syndrome are generally refractory to antiepileptic drugs (AEDs). Seizure-freedom almost never occurs, but many patients experience fewer seizures in late adolescence and adulthood. • Sudden unexplained death in epilepsy (SUDEP) and status epilepticus are more common in patients with Dravet syndrome than most other childhood epilepsy syndromes, and the increased mortality seen in patients with Dravet	Dravet syndrome is a severe epilepsy syndrome beginning in infancy that is associated with significant morbidity due to refractory seizures and cognitive impairment. Even with treatment of the seizures, cognitive impairment persists and is lifelong. Mortality is higher in pediatric patients with Dravet syndrome than the general pediatric population or the overall population with epilepsy. Seizures and seizure-related events are frequent causes of death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	syndrome as compared to the general population is, in part, due to these seizure-related events.	
Current Treatment Options	• The primary objective of treatment of seizures in patients with DS is reduction in frequency of the most incapacitating and injurious seizures (e.g., tonic-clonic seizures, tonic-atonic seizures). • Two drugs are approved by FDA for reduction of seizures in patients with Dravet syndrome: cannabidiol and stiripentol. Many other drugs are used to treat seizures in patients with Dravet syndrome, especially valproic acid (which is generally considered a first-line agent), clobazam, and levetiracetam. Seizures in Dravet syndrome are generally resistant to AEDs (even when used as polytherapy) and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. • Severe adverse drug reactions are reported for many of the approved and/or frequently used drugs to treat seizures in Dravet syndrome, such as drug induced liver injury (cannabidiol), somnolence and sedation (cannabidiol and stiripentol), weight loss/decreased appetite/cachexia (stiripentol), and hematologic abnormalities (stiripentol). Hepatic failure (valproic acid) and serious skin reactions (clobazam) are serious reactions reported in the frequently used drugs.	Two drugs have been shown in controlled clinical trials to reduce convulsive seizures in patients with Dravet syndrome. Other drugs are used off-label. Yet even when taking multiple AEDs, most patients still have frequent seizures. No AEDs have been shown to alter the cognitive impairment in patients with Dravet syndrome. Severe adverse drug effects have been reported with both approved drugs and most of the drugs frequently used off-label and must be considered when choosing an AED treatment, especially in children and adolescents. The treatment armamentarium in Dravet syndrome would benefit from more therapeutic options that are efficacious and well-tolerated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• There are two pivotal trials that demonstrate the efficacy of fenfluramine given orally in patients with Dravet syndrome. One study demonstrates the efficacy of the 0.2 and 0.8 mg/kg/day doses in the absence of concomitant stiripentol and the other study demonstrates the efficacy of 0.5 mg/kg/day in patients taking concomitant stiripentol. The primary endpoint in both studies is the reduction in mean convulsive seizure frequency from baseline to treatment period as compared to placebo. In Study 1, fenfluramine reduced the mean seizure frequency by 70% in the 0.8 mg/kg group and 32% in the 0.2 mg/kg/day group, as compared to placebo. In Study 1504-C2, fenfluramine reduced the mean convulsive seizure frequency from baseline to treatment period by 60% in the fenfluramine group compared to placebo. The findings of the primary endpoint were statistically significant for all fenfluramine groups tested ($p<0.001$ and $p=0.043$, respectively, in the 0.8 and 0.2 mg/kg/day groups in Study 1 and $p=0.0135$ in the 0.5 mg/kg/day in Study 1504-C2). The analysis results were generally consistent across subgroups. • Two key secondary endpoints were statistically significant for all fenfluramine dose groups in both studies and were consistent with the findings of the primary endpoint. These key secondary endpoints assessed the proportion of patients who were 50% responders and the longest interval between convulsive seizures.	Two pivotal clinical trials identified clinically meaningful and statistically significant differences reduction in mean convulsive seizure frequency from baseline in all fenfluramine dose groups (0.2 mg/kg/day and 0.8 mg/kg/day in Study 1 and 0.5 mg/kg/day in Study 1504-c2) compared to placebo. Analyses of key secondary endpoints also favored fenfluramine over placebo. Fenfluramine is an important addition to treatment options expected to provide benefit in the treatment of seizures associated with Dravet syndrome.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Data integrity was a major concern identified in the review of both pivotal trials. Due to poor caregiver compliance with the electronic seizure diaries, device-design and connectivity issues, lack of contingency planning for device failures, and poor monitoring centrally and the sites, some seizure diary data was entered and/or modified in most patients during the trials. It was determined that 8.6% and 9.2% of the total seizure frequency data in Studies 1 and 1504-C2, respectively, were retrospectively changed. Because the source document for most of these modified data were not available for review, the primary and secondary endpoint analyses were performed on the "pre-edited" seizure data.	
Risk and Risk Management	• Decreased appetite - Most frequently reported TEAE in the pooled FEN group of controlled studies and in the 0.5 and 0.8 mg/kg groups (3rd most frequently reported in the 0.2 mg/kg group). - 37% of patients in pooled FEN treatment group, 8% of patients in pooled placebo (PBO) group. - Potentially synergistic effect with STP (has a warning for decreased appetite): reported in 48% of patients in the 0.5 mg/kg (+STP) group and 11% of patients taking PBO+STP. - 1 patient in the 0.8 mg/kg/day group had an SAE of decreased appetite - 2 patients (1 each in 0.8 and 0.5 mg/kg groups) discontinued treatment due to decreased appetite	Depression of appetite and weight loss may be severe and require discontinuation of treatment. Measured weight loss appears to decline with prolonged use. This may be monitored. Somnolence, sedation, and lethargy are effects of central nervous system depression seen frequently in antiseizure drug treatment. These are generally reversible upon discontinuation of treatment. This adverse reaction may be monitored. Neither VHD nor PAH have been observed to date in the Fintepla development program, although both were associated with fenfluramine when previously approved as an anorectic agent. VHD or PAH may be identified by regular monitoring via echocardiograms,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Weight Decreased - 8% of patients in pooled FEN group, 1% of patients in pooled PBO group - 1 patient in the 0.8 mg/kg/day group had an SAE • Weight loss - Measured weight loss during the controlled trials: 2%, 13%, 19% and 26% of patients in the placebo, 0.2 mg, 0.5 mg, and 0.8 mg groups respectively lost ≥7% of their baseline weight by the final visit of the controlled studies. - Weight loss slowed down during the OLE study • Somnolence, Sedation, and Lethargy - 25% of patients in pooled FEN treatment group, 11% of patients in pooled PBO group - 3 SAEs of somnolence (2 in 0.8 mg/kg and 1 in 0.5 mg/kg) - 3 patients (all in the 0.8 mg/kg/day group) discontinued participation due to somnolence - No clear dose response • Valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) - Reported with use of fenfluramine and dexfenfluramine when used as anorectic agents in the 1990's. - Monitoring via echocardiograms during the controlled and OLE studies revealed no findings of VHD or PAH or any valvar abnormalities.	regardless of the presence of signs or symptoms. If findings consistent with either VHD or PAH are present on an ECHO, a determination of benefit vs. risk should be made, if the drug is not discontinued. Because ECHO monitoring is necessary for identifying VHD or PAH, a REMS with ETASU will be necessary, as is a box warning.

1.4. Patient Experience Data

The primary endpoint for the pivotal trials is based on seizure counts, which were recorded by patients and/or caregivers in a diary and reported to the Applicant. Additional patient and/or caregiver reported outcome measures in the trials included measures of quality of life and global impression of change.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	See Sections 6.1 and 6.2 Study endpoints
		X	Observer reported outcome (ObsRO)	See Sections 6.1 and 6.2 Study endpoints

2. Therapeutic Context

2.1. Analysis of Condition

Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy, is a developmental and/or epileptic encephalopathy (DEE), as defined by the International League Against Epilepsy (ILAE).[5] Clinically, it is characterized by refractory seizures of multiple types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression.[6,7] The syndrome typically presents prior to 1 year of age as frequent febrile seizures[8], and patients then develop hemi-clonic, bilateral clonic, and/or generalized tonic-clonic (GTC) seizures before age 2 years.[7,9,10] Other seizure types exhibited by patients with DS include clonic, tonic, atonic, absence, and/or focal seizures. Patients typically present with developmental delay by age 2 years.[7,9] Other neurologic findings include ataxia, pyramidal signs, and interictal myoclonus. Brain imaging is generally normal or non-specific.

[5] Scheffer IE, Berkovic S, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521
[6] Brunklaus A, Zuberi S. Dravet syndrome—From epileptic encephalopathy to channelopathy. Epilepsia, 55(7):979–984, 2014
[7] Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:1-6.
[8] Wang JW, Shi XY, et al. Prevalence of SCN1A mutations in children with suspected Dravet syndrome and intractable childhood epilepsy. Epilepsy Res. 2012 Dec;102(3):195-200.
[9] Dravet C, Bureau M, Oguni H, et al. Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (Eds) Epileptic syndromes in infancy, childhood and adolescence. London: John Libbey, 2005:89–113.
[10] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52 Suppl 2:3-9.

As the patient ages, the course of the disease changes. The seizures in patients with DS evolve over time, beginning with a period of seizures of variable frequency related to fever in the first year, seizures increasing in frequency and types from ages 1 to 5 years (a "catastrophic phase"), and stabilization of seizures after age 5 years.[10] Mortality during childhood and adolescence in patients with DS is about 15% (5-20%), primarily due to status epilepticus in the early years and sudden unexpected death in epilepsy patients (SUDEP) in adolescence and adulthood.[11,12] SUDEP rates in the DS population as a whole (9.32/1000 person-years) are notably greater than in the epilepsy population at-large (1.5-5.1/1000 person-years).[12] Other causes of death are usually indirectly related to the consequences of seizure, especially status epilepticus, and include drowning and traumatic injuries[13]. Seizure-freedom almost never occurs, but most seizures do become less frequent. Some types of seizures (myoclonic and absence) may remit during childhood.[11,13]

The syndrome is relatively rare, occurring in 1/15,700 to 1/40,000 live births in the United States[14,15]. Dravet syndrome accounts for less than 2% of epilepsy in children less than 15 years old[16]. A majority (70-80%) of patients with the clinical syndrome have one or more mutations in the alpha-1 subunit of the voltage-gated sodium channel (*SCN1A*) gene.[6,17,18]

Although treatment of seizures in some patients with DEEs may lead to improved cognition, seizures in patient with DS are generally refractory to antiepileptic drugs (AEDs). Some sodium channel blocking AEDs (carbamazepine [CBZ], oxcarbazepine [OXC], lamotrigine [LTG], vigabatrin [VGB] and phenytoin [PHT]) and GABA re-uptake or GABA enzyme inhibitors (VGB and tiagabine [TGB]) may exacerbate the seizures and are generally avoided.[19,20]

2.2. Analysis of Current Treatment Options

Prior to 2018, there were no approved treatments of seizures associated with DS in the U.S. In June 2018, cannabidiol (CBD) was approved for treatment of seizures associated with Dravet

[11] Akiyama M, Kobayashi K, et al. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia 2010;51(6):1043-1052
[12] Cooper MS, Mcintosh A, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016 Dec;128:43-47.
[13] Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia 2011;52 Suppl 2:44-49.
[14] Hurst DL. Epidemiology of severe myoclonic epilepsy of infancy. Epilepsia 1990;31(4):397-400.
[15] Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet Syndrome in a US Population. Pediatrics 2015 Nov; 136(5):e1310-5
[16] Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. J Child Neurol 2007;22(7):823-828
[17] Claes L, Del-Favero J, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68(6):1327-1332
[18] Depienne C, Trouillard O, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet 2009;46:183–191
[19] Guerrini R, Dravet C, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39(5):508-12.
[20] Brunklaus A, Ellis R, et al. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329–2336

syndrome based on safety and efficacy data collected from a randomized, placebo-controlled pivotal trial of Epidiolex 20 mg/kg/day as compared to placebo. The primary endpoint was the percentage reduction in convulsive seizure frequency from baseline to treatment period as compared to placebo. In patients with DS, CBD reduced the median percentage seizure frequency from baseline to treatment period by 38.9% in the CBD group and 13.3% in the placebo group (p=0.0123).[21] The proportion of 50% responders (key secondary endpoint) was numerically greater in the CBD group (42.6%), compared with the placebo group (27.1%) with an OR=2.0 (p=0.0784).

Stiripentol (STP) was approved for treatment of seizures associated with DS in patients 2 years of age and older taking clobazam by the U.S. FDA in September 2018. This approval was on the basis of 2 randomized, placebo-controlled trials comparing STP 50 mg/kg/day to placebo in the reduction of seizures associated in patients with DS. Almost all patients were taking concomitant valproate and clobazam. Both of these were small studies with a total of 64 patients. In the STICLO France study, the responder rate for STP treatment arm was 71.4% compared to 5% in the PBO arm (p<0.00001). In the STICLO Italy study the responder rate in the STP treatment arm was 67% compared to 9% in the PBO arm (p=0.009).[22]

A number of drugs are used off label as part of standard of care with varying degrees of effectiveness. The most commonly used AEDs in the treatment of seizures are clobazam (CLB) and valproic acid (VPA). Adjunctive treatment with VPA and/or CLB results in a 50% reduction in seizures in about 25% of patients[23,24]. In an open-label study of adjunctive valproic acid and clobazam therapy in patients with DS, 1/24 and 2/16 patients treated with VPA or CLB respectively were seizure free for a 12-week trial period[24]. Levetiracetam was studied in a small open-label single arm study in patients with DS with a reported responder rate of 64%.[25] The ketogenic diet may be helpful[26] and is typically used as an adjunct to pharmacologic treatment(s).

[21] NDA 210365 Epidiolex clinical review (Natalie Getzoff, MD), dated 6/14/2018
[22] NDA 206709 Diacomit clinical review (Steven Dinsmore, MD), dated 5/29/2018
[23] Inoue Y, Ohtsuka Y, et al. Stiripentol open study in Japanese patients with Dravet syndrome. Epilepsia 2009;50(11):2362-2368.
[24] Inoue Y, Ohtsuka Y. Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. Epilepsy Res 2014;108(4):725-731.
[25] Striano P, Coppola A, Pezzella M, et al. An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. Neurology 2007;69:250-254
[26] Caraballo RH, Cersosimo RO, et al. Ketogenic diet in patients with Dravet syndrome. Epilepsia 2005;46(9):1539-1544.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved treatments					
Cannabidiol (CBD)	Treatment of seizures associated with DS or Lennox-Gastaut syndrome (LGS) in patients 2 years and older	2018	Oral Solution Start 5 mg/kg/day, titrate to 10-20 mg/kg/day	Primary endpoint was median change in convulsive seizure frequency (baseline to treatment) CBD -39%, PBO -13% (p=0.0123). Key secondary endpoint: ≥50% Responder Analysis PBO 27%, CBD 43% (p=0.078)	Transaminase elevations identified in 13% of cannabidiol patients compared to 1% of PBO patients. Somnolence and sedation noted in 32% of cannabidiol compared to 11% of PBO patients.
Stiripentol (STP)	Treatment of seizures associated with DS in patients 2 years and older taking clobazam	2018	Capsules and packet for oral suspension Dose: 50 mg/kg/day	Primary endpoint was ≥50% Responder Analysis (baseline to treatment): STICLO France STP 71%, PBO 5% (p=0.0123) STICLO Italy STP 67%, PBO 9% (p=0.009)	Warning for somnolence, decreased appetite/weight loss, and neutropenia/ thrombocytopenia.
Other Treatments, 1st Line					
Clobazam (CLB)	Adjunctive treatment of seizures associated with LGS in patients 2 years of age or older	2011	Begin 5 mg/day, titrate up to 20 mg/day	Limited amount of data on the efficacy of clobazam in DS, single retrospective study	Behavioral disinhibition, sedation, ataxia and increased salivation.
Valproic acid (VPA)	Monotherapy and adjunctive therapy of complex partial seizures; sole and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients	1978	Start at 10 to 15 mg/kg/day, increasing at 1-week intervals by 5 to 10 mg/kg/week until seizure control or limiting side effects	There is minimal literature on its use in DS (level 4), and in retrospective studies responder rates (>50% reduction	Potential for several severe adverse effects, including hepatotoxicity (particularly with underlying mitochondrial disease), hyperammonemia, pancreatitis and thrombocytopenia.

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
	with multiple seizure types that include absence seizures			in seizure frequency) were 22.2-48%.	Additionally, other adverse effects may include decreased or increased appetite, tremor (at higher doses), hair loss and sedation.
Other Treatments, 2nd and 3rd line options					
Topiramate (TPM)	Initial monotherapy for treatment of partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures in patients ≥2 years Adjunctive therapy for the treatment of POS, PGTC, or seizures associated with LGS in patients 2 years of age and older	1996	250-400 mg daily, divided BID, weight-based dosing for pediatric patients	Observational, open label, and retrospective study have shown responder rates of 35-78%.	Warnings for adult and pediatric patients: Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Cognitive/ Neuropsychiatric Adverse Reactions (lower in peds than adults), Hyperammonemia and Encephalopathy, Kidney Stones,
Levetiracetam (LEV)	POS in patients one month of age and older with epilepsy, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, PGTC seizures in patients 6 years of age and older with idiopathic generalized epilepsy.	1999	Starting at 7mg/kg twice daily in children 1 month to < 6 months Up to 500mg BID in adults	Reported to have a responder rate of 64% in a single open label prospective study	Warnings: Behavioral abnormalities and psychotic symptoms, somnolence and fatigue, anaphylaxis and angioedema, SJS and TEN, coordination difficulties, reduction in WBC and neutrophil counts (statistically sig worse in Keppra-treated pediatric patients than those on placebo), hypertension (particularly in the 1 mo to 4 yr study)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fenfluramine hydrochloride was originally approved in the United States under the trade name Pondimin in 1973 for use as an anorectic agent and was prescribed both alone and in combination with phentermine ("fen-phen") as an appetite suppressant for the treatment of adult obesity. Fenfluramine and its d-enantiomer form (dexfenfluramine, Redux) were withdrawn from the U.S. market in 1997 due to drug-related left-sided cardiac valvular disease. In September 2015, the FDA determined that fenfluramine was deemed "withdrawn from the U.S. market due to reasons of safety".[4] See Section 8.5.1 for a detailed discussion of fenfluramine-associated valvular heart disease and pulmonary arterial hypertension, both of which led to the withdrawal of fenfluramine from the U.S. market for reasons of safety.

The initial approval of fenfluramine as an appetite suppressant in adult patients was based on data from approximately 13 clinical trials. Many of these trials were performed at a single site and included as few as 20 patients. The largest study included 120 patients. Not all of these trials were placebo-controlled, and some included an active control (e.g., dextro-amphetamine). The most common dose studied was 60 mg/day (20 mg TID), though maximum dose was 120 mg/day. The most common reported AEs in adult patients treated for obesity were drowsiness (15%) and diarrhea (16%).

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 125797 was submitted to FDA on August 28, 2015 for a study of the safety and efficacy of fenfluramine in the treatment of convulsive seizures associated with Dravet syndrome.

Significant clinical interactions between FDA and the Applicant for the Dravet syndrome indications include the following:

- Pre-IND meeting under IND-(b) (4) (22 OCT 2013)
- Orphan Designation (13-4146) for treatment of Dravet syndrome, granted 20 DEC 2013
- Type C Pre-IND Meeting (16 MAY 2015): Meeting held prior to submission of the initial DS protocol to IND-125797, during which clinical pharmacology issues and specific trial design concerns (e.g., dosing and titration schedule), as well as adequate monitoring for VHD and PAH were discussed. The Applicant proposed initial dosing of (b) (4)
- Fast-Track Designation granted 8 JAN 2016
- EOP2 meeting (granted as Type C WRO; 21 OCT 2016): Sponsor requested clarification of CMC, clinical pharmacology and statistical questions. The Sponsor was notified that a food effect study and a complete QTc study would be required. PK samples after all serious/severe AEs was requested. The plan to reconfigure Studies 1501 (U.S.) and 1502 (non-U.S.) into Studies 1 and 2 based on consecutive enrollment might impact the

interpretability of the study results.

- Breakthrough Therapy Designation granted 5 FEB 2018 for "ZX008 (fenfluramine HCl) for the treatment of seizures associated with Dravet syndrome".
- Initial Breakthrough Therapy meeting (24 APR 2018): CMC, clinical pharmacology, human factors, and clinical issues discussed. On face the proposed clinical data package and amount of safety data would be acceptable for submission of the NDA. Inclusion of data from all patients enrolled in the long-term safety study would be needed (not just the ones from Studies 1 and 1504-C2). Concerns reiterated about potential issues with interpretability of Study 1 (matter of review). FDA conveyed the need to submit the Use Related Risk Assessment which should address the syringe question.
- Pre-NDA meeting (21 NOV 2018): Clinical key points: 1) FDA agreed to review Zogenix's proposed approach to categorization or binning of the responder rate; indicated they prefer the approach used in recently approved labeling of other products (e.g., Diacomit and Epidiolex); 2) FDA requested that Zogenix provide the data and a rationale for the clinical meaningfulness of the longest seizure-free interval for review; 3) FDA requested that Zogenix provide justification for utilizing CGI as an outcome measure. CMC issues also discussed.
- Pediatric Written Request
- Original NDA submitted on (5 FEB 2019) for Fintepla for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. A refuse-to-file letter was issued on 5 APR 2019 due to 1) failure to submit chronic nonclinical toxicity studies to and incorrect SAS efficacy datasets and the need to "conduct an extensive data quality assessment to ensure the accuracy of trial results" prior to resubmitting the NDA.
- Breakthrough Therapy Designation rescinded as two drugs have been approved for the same indication and the Applicant has not demonstrated that their drug is superior to both.
- Type A meeting (7 JUN 2019): FDA stated that, on further internal discussion, the lack of chronic toxicity studies is a review issue rather than a filing issue. Zogenix can refile the NDA as a 505(b)(2). Applicant provided a detailed discussion of the dataset error issues. ISS and ISE will use the original NDA cutoff dates, but the 120-day safety update will update the data. Since the submission will partially fill the WR, the NDA resubmission should qualify for priority review.
- NDA resubmission on 25 SEP 2019
- Major Amendment granted on 25 FEB 2020

3.3. Foreign Regulatory Actions and Marketing History

Fenfluramine is not currently marketed in any country. It was withdrawn from the wider market in the late 1990's for reasons of safety as described above.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please see Dr. Grandinetti's review for a complete discussion of OSI's findings.

The FDA inspections of four sites and the EMA inspection (shared with FDA under a Memo of Understanding) identified significant data reliability concerns. These concerns were related primarily to retrospective collection of seizure data and modification of the electronic diary (eDiary) data in both pivotal trials, nonreporting of protocol deviations by the sites to the Applicant and by Applicant to FDA, and drug accountability issues during the pivotal trials.

The protocols for both studies prespecified that eDiaries would be used to collect information from questionnaires and document the daily seizure counts and end-of-day seizure status (yes or no) on a contemporaneous basis. However, the FDA inspections of 4 sites, as well as the EMA inspection of the Applicant, identified that seizure and end-of-day data were collected retrospectively and entered into the eDiary database using a data clarification request (DCR) process as much as a year after the original date of the event(s). The reported source records for the retrospective eDiary data included paper diaries, paper calendars, Seizure Diary Entry Template (paper forms completed by site personnel during interviews with caregivers or after review of caregivers' diaries/calendars), End of Day Review Diary Capture Forms (paper forms similar to the Seizure Diary Entry Template but used to record end of the day seizure vs. no-seizure response based on the presence or absence of seizures on a specific day), other caregiver or legally authorized representative's (LAR's) seizure notes, and medical records/ physician notes.

As noted by Dr. Grandinetti, the *root cause of the retrospective collection of the eDiary data included the following:*

- *Higher than expected amount of missing eDiary data*
- *Poor caregiver compliance of eDiaries*
- *eDiary device design, connectivity, and transmission issues experienced during the conduct of the trial*
- *Lack of contingency plans for collecting eDiary data when devices failed or when there were connectivity and transmission issue*
- *Inadequate centralized and ineffective on-site monitoring efforts that were necessary to proactively identify and follow-up on missing data and other problems that may be indicative of systemic or significant issues*

Source records used for the retrospective data modifications and entries were not reliably retained by study sites. Discrepancies were noted in the verification of the source records against the data listings submitted to the NDA. Multiple Information Requests (IRs) were sent to the Applicant in an effort to understand the extent of the retrospective data additions and modifications and verify the veracity of the data modifications via source data. In a response to an IR, dated 13 January 2020, Zogenix provided an extensive listing of all retrospective seizure data for both studies. The information in this response disclosed that retrospective seizure and end-of-day eDiary data were collected in 96% (114/119) of randomized patients in Study 1 and 90% (78/87) of randomized patients in Study 1504-C2. As determined by Dr Xiangmin Zhang (Office of Biostatistics), the retrospective seizure data involved 8.6% and 9.2% of the total seizure frequency data in Studies 1 and 1504-C2, respectively. Two patients from each study were excluded from the pre-DCR analyses, because baseline seizure frequencies were insufficient for inclusion in the studies, based on the randomization inclusion criterion requiring 6 convulsive seizures during the baseline period. Dr. Zhang reanalyzed the primary and key secondary efficacy endpoints for both studies using datasets containing data without retrospective editing; the outcomes remained statistically significantly in favor of the fenfluramine treatment groups. See Sections 6.1.2 and 6.2.2 for discussion of the efficacy results for Studies 1 and 1504-C2, respectively.

Four clinical sites were chosen for inspection, primarily based on numbers of enrolled patients, site efficacy, reported protocol deviations, and prior history of inspections (or lack thereof). Two of the sites were in the U.S. (0107 and 0109), and two were in Europe (1001 and 0701).

- Site 0107 (Study 1): Dinesh Talwar, MD (PI), Tucson, AZ. 4 patients were screened and enrolled. Twenty-three (23) protocol deviations were identified in the source records by the clinical investigator that were not reported to FDA. The most significant unreported protocol deviation led to dosing of >2 times the correct dose. End-of-day eDiary data had been collected retrospectively on all 4 patients and could not be sufficiently verified using source (paper) documents.
- Site 0109 (Studies 1 and 1504-C2): Elaine Wirrell, MD (PI), Rochester, MN. For Study 1, 5 patients were screened, and 3 were randomized. For Study 1504-C2, 4 patients were screened and randomized. A portion of the eDiary data was collected retrospectively for all 3 randomized patients in Study 1 and for 3 of the 4 randomized patients in Study 1504-C2. The eDiary data collected retrospectively in all 7 patients could not be verified because the source documents were unavailable.
- Site 0701 (Study 1): Marina Nikanorova, MD (PI), Dianalund, Sjalland, Denmark: 9 patients were screened, 7 enrolled, and 6 completed the study (1 discontinued early due to lack of efficacy). A dosing error occurred in Subject (b) (6) (placebo), which was not initially reported to FDA (although it was included in the 13 MAR 2020 IR response). A portion of study medication, seizure, and end-of-day eDiary data from all 7 patients at this site had been collected retrospectively. The inspection noted that many of the source records needed to verify the retrospective entries were missing, incomplete, and or contained discrepant information. Other issues identified during the inspection included multiple seizure events experienced on a single date or on multiple dates on

one form, which were incorrectly interpreted as one seizure event by the ERT personnel inputting the retrospective data into the electronic database. Paper records were generally incomplete.

- Site 1001 (Study 1504-C2): Rima Nabbout, MD (PI), Paris, France. 13 patients were screened and 11 were randomized. A portion of study medication, seizure, and end-of-day eDiary data from all 11 patients at this site had been collected retrospectively. The inspection noted that many of the source records needed to verify the retrospective entries were missing, incomplete, and or contained discrepant information.

Reviewer's comment: There were substantial data integrity issues in both Studies 1 and 1504-C2, as identified in the site inspections and in the EMA inspection of the Applicant. The most concerning of these include extensive retrospective new seizure data entries and modifications of previously entered seizure data. The source data used by the sites in the retrospective data collection (e.g., paper diaries, calendars, capture forms) were either unavailable for review during the inspection or, if available, demonstrated discrepancies when compared to the seizure dataset. Other inspection-related issues included non-reporting of protocol deviations, misclassification of major protocol deviations as minor, and inadequate drug accountability records.

The primary and key secondary efficacy endpoints were reanalyzed using a "pre-edited" dataset in which the seizure and end-of-day diary data were reverted to values consistent with what they would have been prior to the retrospective modifications. Because of the inability to verify the source data for most of the retrospective seizure data entries, the primary efficacy and key secondary efficacy endpoints were evaluated using the "pre-edited" dataset. The identification of these issues and the need for revised datasets occurred over 3 months' time and based on responses to several IR's sent to the Applicant. The IR response that provided usable datasets for analyses of the primary endpoints for both Studies 1 and 1504-C2 was received on February 23, 2020. Because these data were necessary for FDA's analyses of the primary efficacy endpoints, this submission was considered a major amendment to the application, and the user fee goal date was extended by three months to June 25, 2020.

4.2. Product Quality

Please see the OPQ review for any issues related to product quality.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Fisher's review for any issues related to nonclinical pharmacology/toxicology.

4.5. Clinical Pharmacology

The Clinical Pharmacology review had not been finalized at the time the clinical review was completed. Please see the Office of Clinical Pharmacology (OCP) review for any issues related to pharmacokinetics.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant included 8 studies in the tabular listing of all clinical studies in section 5.2 of the NDA application. (b) (4)

Two of these studies are pivotal trials in patients with DS (Studies 1 and 1504-C2), one is a long-term open-label safety study (Study 1503), and one is an open-label PK study in patients with DS (Study 1504-C1). The other three studies were conducted in healthy volunteers to assess drug-drug interactions (DDI), effect on ECG, and food effects.

Table 2: Listing of Clinical Trials Relevant to this NDA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study 1 Study 1501 NCT-02682927 Study 1502 NCT-02826863	Randomized, double blind, placebo-controlled	FEN oral solution 0.2 or 0.8 mg/kg/day (divided BID) vs equal volume of placebo. Titration: Initial dose for both FEN groups: FEN 0.2 mg/kg/day. 0.8 mg/kg/day group increased to 0.4 mg/kg/day on day 5 and to 0.8 mg/kg/day on day 9.	Primary: Change in the mean convulsive seizure frequency (MCSF) per 28 days during the titration + maintenance (T+M) periods compared with the baseline period for the 0.8 mg/kg/day group. Key secondary endpoints: • Change in the MCSF per 28 days during treatment (T+M) compared with the baseline period for the 0.2 mg/kg/day group. • The proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency (both dose groups). • Comparison between treatment and placebo groups in the longest convulsive seizure-free interval during T+M.	Baseline: 6 weeks Titration: 2 wks Maintenance: 12 wks Taper/ Transition: 2 weeks	173 screened 119 randomized FEN 0.8 mg/kg/day: 40 FEN 0.2 mg/kg/day: 39 PBO: 40 Screen failures: 54	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 6 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks. No patients taking concomitant STP	38 centers in 10 countries: USA (16), GBR (5), DEU (7), ITA (4), AUS, (2), BEL (1), DEN (1), CAN (1), ESP (1)
Study 1504-C2 NCT-02926898	Randomized, double blind, placebo-controlled	FEN oral solution 0.5 mg/kg/day (divided BID) vs equal volume of placebo.	Primary: Change in the mean convulsive seizure frequency (MCSF) per 28 days during T+M periods compared with the baseline	Baseline: 6 weeks Titration: 2 wks Maintenance: 12 wks Taper/ Transition:	115 screened 87 randomized FEN 0.5 mg/kg/day: 43 PBO: 44	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 6	25 centers in 7 countries: USA (5), GBR (4), DEU (2), FRA (7), NLD, (2), CAN (2),

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Titration: Initial dose FEN 0.2 mg/kg/day, increased to 0.4 mg/kg/day on day 8 and to 0.5 mg/kg/day on day 15.	period. Key secondary endpoints: • The proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency (both dose groups). • Comparison between treatment and placebo groups in the longest convulsive seizure-free interval during T+M.	2 weeks	Screen failures: 28	convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks. All patients taking concomitant STP	ESP (3)*
Study to Support Safety							
Study 1503 NCT-02823145	Open-label, uncontrolled, long-term safety	FEN oral solution Flexible dosing 0.2-0.8 mg/kg/day (divided BID)	Primary: Assess the long-term safety and tolerability of FEN.	3 years	232 enrolled	2-18 years with a clinical diagnosis of DS and refractory seizures, enrolled into Studies 1, 1504-C1, or 1504-C2.	54 centers in 11 countries: USA (19), GBR (6), DEU (7), FRA (5), NLD, (2), CAN (2), ESP (3), ITA (6), BEL (1), AUS (3), DEN (1)*
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
Study 1504-C1 NCT-02926898	Multicenter, open-label, partially randomized, multiple dose, PK study	1) Regimen 1: CLB + VPA + ZX008 0.2 mg/kg; 2) Regimen 2: CLB + VPA + ZX008 0.4 mg/kg; 3) Regimen 3: CLB + VPA + STP + ZX008 0.2	• Assess the PK profile of FEN (single oral dose) with CLB + VPA or with CLB + VPA + STP in subjects ages 2 to 18 years of age with Dravet syndrome, via the use of summary statistics • Model PK of FEN in single-dose regimens	Baseline: 2 weeks Dosing: Single dose Transition: 2 weeks OLE: 6 months	20 screened 18 randomized Regimen 1: 3 Regimen 2: 5 Regimen 10	2-18 years with a clinical diagnosis of DS and refractory seizures, CLB, VPA, and STP at a stable dose for ≥ 4 weeks.	

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		mg/kg.	using FEN/norFEN concentration-time data				
Study 1505 N/A	Two Part, Randomized, Open-label, Single-dose, 3-way Crossover Study	0.8 or 0.2 mg/kg/day divided BID	To assess the PK profile of FEN administered as a single oral dose with and without STP regimen (STP/CLB/VPA), and in fed and fasted state	7 days	17	Healthy volunteers	
Study 1603 N/A	Randomized, double-blind, double-dummy, controlled, 3-arm, 4-trt, parallel study	15 or 60 mg divided BID	Evaluate effects of multiple doses of therapeutic and supratherapeutic FEN on the heart rate-corrected QT interval (QTcF)	1-8 days	180	Healthy volunteers	
Study 1604 N/A	Open-label sequence, DDI study	FEN 0.4 mg/kg single dose Up to 700 mg BID of CBD	To assess the PK profile of FEN administered as a single oral dose with and without CBD regimen	1-28 days	32	Healthy volunteers	

*United States: USA, Australia: AUS, Belgium: BEL, Canada: CAN, Denmark: DEN, France: FRA, Germany: DEU, Great Britain: GBR, Italy: ITA, Netherlands: NLD, Spain: ESP

5.2. Review Strategy

An efficacy determination was made by evaluating the results from two double-blind, placebo-controlled trials, both in patients with DS, one of which included patients not taking concomitant STP (Study 1) and the other in patients who were all taking STP concomitantly (Study 1504-C2). This reviewer assessed the primary endpoint by examining the source data provided by the Applicant.

Statistical analysis of the data was performed and reported by Dr. Xiangmin Zhang and was used as the basis of the clinical efficacy analyses in this clinical review.

Safety analyses were performed primarily on a pooled dataset of patients from the blinded phases of Studies 1 and 1504-C2. Because the study designs for Studies 1 and 1504-C2 were sufficiently similar, the safety data from the blinded portions of these studies could be combined into a pooled dataset, allowing for analyses on a larger number of patients.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 1

6.1.1. Study Design

Title

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Overview and Objective

Study 1 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of fenfluramine (ZX008) in patients with refractory seizures associated with Dravet syndrome.

The objectives of this study were as follows:

- Primary: *To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between the Baseline period and the combined Titration and Maintenance (T+M) periods.*
- Key Secondary:
  - *To demonstrate that ZX008 0.2 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome based on change in the frequency of convulsive seizures between the Baseline period and T+M.*
  - *To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are*

(independently) superior to placebo on the following endpoints.
  - *The proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency.*
  - *The longest convulsive seizure-free interval*
- Safety objective: *To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), electrocardiograms (ECGs), echocardiograms (ECHOs), body weight, and cognitive function (cognitive function was assessed using the age-appropriate versions of the Behavior Rating Index for Executive Function Scale [BRIEF])*

There were a number of other secondary and exploratory objectives.

Trial Design

Study 1 is comprised of about half of the planned number of patients who were enrolled into two separate studies (Studies 1501 and 1502). Studies 1501 and 1502 have been conducted in parallel with Study 1501 enrolling patients from approximately 30 study sites in North America and Study 1502 enrolling patients at approximately 30 study sites in Europe and Australia. Because of slow recruitment into both studies, the Applicant proposed prospectively to combine the first 120 patients who were consecutively randomized into either Studies 1501 or 1502 into a combined study and analyze the efficacy and safety.

- **Basic Study Design**
  Study 1 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of fenfluramine conducted at 38 centers worldwide. The Applicant planned to combine the first 120 patients consecutively randomized into either Studies 1501 or 1502 into Study 1. This study was conducted to test the clinical efficacy, safety, and PK of fenfluramine oral solution in patients with seizures associated with Dravet syndrome. The total duration of patient participation in the study was approximately 22 weeks with duration of treatment about 16 weeks. The study consisted of a Baseline Period (6 weeks), a Treatment Period (titration [2 weeks] plus maintenance [12 weeks]), and a Taper/Transition Period (alternatively, patients enrolled in an open label, long-term extension [LTE] study).

  The general design of Study 1 was similar to other pivotal trials evaluating efficacy of AED treatments in general and other DS studies in particular.

- **Trial location**
  Study 1 was conducted in the U.S., Canada, Australia, and Europe (Great Britain, Germany, Italy, Belgium, Denmark, and Spain). The patient population and treatment regimen in Europe and Australia is expected to be similar to that in the U.S.

- **Choice of control group**
  The Applicant used a concurrent placebo control as the comparator group, as recommended in FDA Guidelines for the Clinical Evaluation of Antiepileptic Drugs (Adults and Children)[27]. At the time that this trial commenced, there was no approved treatment for seizures associated with DS in the United States, and comparison to placebo (standard of care) was deemed appropriate.

- **Diagnostic criteria**
  Patients were enrolled if they had a "documented medical history to support a clinical diagnosis of Dravet Syndrome" – a clinical diagnosis – a variety of treatment-resistant seizures that began in the first year of life (including convulsive seizures) and cognitive decline or developmental delay. Although patients were tested for genetic anomalies (most importantly SCN1A mutations), presence of such mutations were not required for inclusion in the study, which is consistent with the currently accepted clinical diagnosis of DS.

- **Key inclusion/exclusion criteria**
  Inclusion Criteria:
  1. Age between 2 and 18 years
  2. Females of childbearing potential must not have been pregnant or breast-feeding and must have had a negative urine pregnancy test. Patients must have been willing to use medically acceptable forms of birth control, which included abstinence, while being treated on this study and for 90 days after the last dose of study drug.
  3. Have a documented history "*to support a clinical diagnosis of*" DS, with convulsive seizures not completely controlled by current AEDs.
  4. Must have met all of the following:
     a. *Onset of seizures in the first year of life in an otherwise healthy infant.*
     b. *A history of seizures that were either generalized tonic-clonic or unilateral clonic or bilateral clonic, and were prolonged.*
     c. *Initial development was normal.*
     d. *History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.*
     e. *Lack of alternative diagnosis*
  5. Must have met ≥ 1 of the following:
     a. *Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal developed after the first seizure type.*
     b. *Prolonged exposure to warm temperatures induced seizures and/or seizures were associated with fevers due to illness or vaccines, hot baths, high levels of activity, and sudden temperature changes, and/or seizures were induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.*

[27] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071582.pdf

c. *Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis).*

6. Must have experienced ≥4 convulsive seizures (i.e., tonic, clonic, tonic-clonic, tonic-atonic) per 4-week period for the past 12 weeks prior to Screening.
7. Must be taking one or more AEDs at a dose which has been stable for at least four weeks.
8. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for four weeks prior to screening and were expected to remain stable throughout the study.
9. Informed consent (and assent if possible) were obtained.

Exclusion Criteria:

1. Known hypersensitivity to fenfluramine hydrochloride or any of the excipients in the study medication.
2. Pulmonary arterial hypertension.
3. Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, or stroke.
4. Current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration > 1 month.
5. At imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must have been excluded if they reported suicidal behavior in the past 6 months, as measured by the C-SSRS at Screening or Baseline, which included suicidal ideation with intent and plan (Item #5). If a subject reported suicidal ideation on Item 4 without specific plan, and the investigator felt that the subject was appropriate for the study considering the potential risks, the investigator must have documented appropriateness for inclusion, and discussed with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Current or past history of glaucoma.
7. Moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [ULN] and/or elevated bilirubin < 2xULN) may have been entered into the study, after review and approval by the Medical Monitor in conjunction with the Sponsor, with consideration of potential cause, concomitant medications, and other risk factors.
8. Receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally acting noradrenergic agonist; or cyproheptadine.
9. Currently receiving or had received STP in the past 21 days prior to screening.
10. Currently taking CBZ, OXC, eslicarbazepine (ESL), phenobarbital [PHB], or PHT, or had

taken any of these within the past 30 days, as maintenance therapy.
11. Subject was unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Baseline period and throughout the study.
12. Subject had positive results on the urine tetrahydrocannabinol (THC) Panel or the whole blood cannabidiol (CBD) at the Screening Visit.
13. Subject had participated in another clinical trial within the past 30 days.
14. Subject was currently receiving an investigational product.
15. Subject was unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
16. Subject had a clinically significant condition, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Randomization Inclusion Criteria

1. Approved for study inclusion by the Epilepsy Study Consortium.
2. Did not have a cardiovascular or cardiopulmonary abnormality based on screening ECHO, ECG, or physical examination, including but not limited to trace mitral or aortic valve regurgitation or signs of pulmonary hypertension, and was approved for entry by the central cardiac reader.
3. Had a stable baseline with ≥ 6 convulsive seizures during the 6-week Baseline period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks.
4. Parent/caregiver had been compliant with diary completion during the Baseline period, in the opinion of the investigator (e.g., at least 90% compliant).

Reviewer's comment: The eligibility criteria for Study 1 are reasonable.

- **Dose selection**

The 0.2 and 0.8 mg/kg/day doses of FEN used in Study 1 were based on open label safety and efficacy data from published studies of a long-term case series (n=14) of FEN used to treat seizures in patients with DS in Belgium (Study ZXIIS2015-04). In these published studies, the mean dose was 0.34 mg/kg/day (range 0.1-1.0 mg/kg/day), divided BID with a maximum of 20 mg BID. All patients received polytherapy (all were on VPA, some were on 3 or more AEDs). No patients discontinued treatment in these two studies because of adverse events. Frequency of cardiac monitoring was unclear in these studies. Six patients had "slightly thickened" valves, although no valvulopathy or cardiac symptomatology was reported. Of note, higher doses (up to 3.6 mg/kg/day) were administered in published studies of FEN used to treat other indications, including autism and ADHD. Doses in Study 1 were selected within the range used in Study ZXIIS2015-04, trading off a need to establish efficacy (0.8 mg/kg/day) as well as a desire to identify a minimally effective dose, especially in younger patients (0.2 mg/kg/day).

- **Study treatments**
  Subjects randomized to the FEN treatment group received daily doses of FEN oral solution (1.25, 2.5, or 5 mg/mL) at 0.2 or 0.8 mg/kg/day, divided BID. Titration schedule is summarized in Table 3 below. Patients in the placebo arm received equal volumes of placebo oral solution using an identical titration schedule.

Table 3: Titration schedule, Study 1

Randomized Group	Titration Step 1 Study Days 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

Please refer to the Office of Pharmaceutical Quality (OPQ) review for discussion of the product formulation used for the active study arm.

- **Assignment to treatment**
  At the initial screening visit, a unique patient number was assigned to each patient. Patients were randomly allocated to FEN 0.2 mg/kg/day, FEN 0.8 mg/kg/day, or equivalent volume of placebo using an interactive web response system (IWRS).

Reviewer's comment: Patients were randomized after completion of the 6-week baseline period, as they were required to have ≥6 convulsive seizures during this time. Patients who did not have sufficient seizures (or were non-compliant with seizure recording) during the baseline were considered screen failures. This is consistent with other AED trials.

Randomization was stratified by age group (<6 years, ≥6 years) and was performed globally.

- **Blinding**
  The IMP was provided in 100 mL amber glass bottles labeled "GWP42003-P Oral Solution or Placebo". The identity of the IMP assigned to patients was held by the IVRS/IWRS. The PI at each site, or his/her designee, was responsible for ensuring that information on how to access the IVRS/IWRS was available to the relevant staff in case of an emergency and unblinding was required.

Reviewer's comment: The described methods of blinding appear adequate. The primary endpoint of change in convulsive seizure frequency could potentially be influenced by unblinding, in that an unblinded caregiver could report seizures differently based on assumption of treatment allocation. Even so, seizure counts remain the most clinically relevant outcome measure of efficacy of a seizure treatment, and the outcome measure/endpoint is standard in AED treatment trials.

This potential for reporting bias is complicated by the retrospective reporting of seizures identified in the EMA inspection and the OSI review. See Section 4.1 for further discussion.

- **Dose modification, dose discontinuation**
  Patients were to continue on a stable dose after titration. However, in the case of a poorly tolerated dose during the maintenance period, the investigator was permitted to temporarily or permanently reduce the dose for the remainder of the study. If an unacceptable AE occurred at any time during titration, dosing was to be suspended or amended as advised by the investigator, until the event resolved. Such dose modifications were captured in the CRFs.

  See Section 8.5.1 below for discussion of thresholds for DSMC assessment of patients based on ECHO criteria. These thresholds were discussed extensively with the Agency prior to commencement of Studies 1501 and 1502.

- **Administrative structure**
  Investigators at 34 study centers in Study 1501 and 33 sites in Study 1502 worldwide received IRB/IEC approval to participate in this study, and 38 centers randomized patients into Study 1. Safety data were reviewed on an ongoing basis by the Applicant's Medical Monitor and by an independent Data Safety Monitoring Committee (IDSMC). An independent study consortium evaluated all patients for the DS diagnosis and verified the seizure types of screened patients.

- **Procedures and schedule**
  The following table from the Applicant summarizes the schedule of study visits, baseline period, treatment period, taper period, and follow-up period.

Table 4: Schedule of Assessments, Study 1

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Follow-up[c]	Cardiac Follow-up
	Screening	2 (Phone)	Random-ization	Titration Period			Maintenance Period							
Visit Number	1		3		4, 5 (Phone)	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	-42 to -41	-21	-1	1	4, 8	15	29	43	57	71	85	99	113	
Informed Consent	X													
Inclusion/Exclusion Criteria	X		X											
Demographics	X													
Medical/Neurological History	X													
Epilepsy history	X													
Collect retrospective seizure diary data	X													
Prior Medication	X		X											
Physical Examination, complete	X		X									X		X
Physical Examination, abbreviated						X		X		X				X
Neurological Examination, complete	X											X		
Neurological Examination, abbreviated			X			X								
Vital signs	X		X			X		X		X		X		
Weight, Height, BMI	X		X			X		X		X		X		
12-lead ECG	X		X									X		X
Doppler ECHO	X									X[d]				X
Urine pregnancy test	X[e]		X[e]			X[e]		X[e]		X[e]		X[e]		
Clinical laboratory evaluation (hematology/ clinical chemistry/UA, etc.	X		X			X		X		X		X		
Plasma sample for ZX008 PK								4X[f]						
Plasma sample for background AEDs			X[g]			X[g]		X[g]				X[g]		
Urine THC Panel	X		X			X		X		X		X		

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Follow-up[c]	Cardiac Follow-up
	Screening	2 (Phone)	Random-ization	Titration Period			Maintenance Period							
Visit Number	**1**		**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Tanner Staging (>7 years old)			X									X		
Subject Diary	D	R	C/R/D		R	C/R/D	R	C/R/D	R	C/R/D	R	C/R/Dh	C/R	
Epilepsy genotype panel	X													
Study Medication			D		R[i]	C/R/D	R	C/R/D	R	C/R/D	R	C/R/Dh	C/R	
C-SSRS	X		X			X		X		X		X		
CGI-I (parent/caregiver)						X		X		X		X		
CGI-I (principal investigator)						X		X		X		X		
Daytime Somnolence NRS			X					X				X		
Sleep Disruption NRS			X					X				X		
Vineland Adaptive Behavior Scale II			X					X				X		
QOLCE			X					X				X		
CHU9D			X					X				X		
EQ-5D-5L (QoL of parent/ caregiver)			X									X		
HADS (QoL of parent/ caregiver)			X					X				X		
Randomize subject			X											
First Day of Study Drug Administration				X[j]										
Daily Diary Completion	X													
Concomitant Medication				X										
Adverse events	X													
AESI	X													X

Abbreviations: AED = antiepileptic drug; AESI = Adverse events of special interest; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Function; BRIEF-P = BRIEF scale preschool; C = Collect; D = Dispense; ECG = electrocardiogram; EOS = end of study; ET = early termination; EQ-5D- 5L = standardized measure of health status; HADS = Hospital Anxiety and Depression Scale; PedsQL = Pediatric Quality of Life Inventory; QoL = quality of life; QOLCE = Quality of Life in Childhood Epilepsy; R = Review.

- **Concurrent medications**
  Patients had to be on at least one AED at a stable dose during the trial. All non-pharmacological therapies for epilepsy (e.g., ketogenic diet, VNS) also had to be stable for four weeks prior to screening and remain so throughout the duration of the study.

  Any medication, other than the IMP, taken during the study was to be recorded on the appropriate Case Report Form (CRF).

  Prohibited therapies during the study period were as follows:
  - AEDs: PHT, CBZ, OXC, ESL, retigabine/ezogabine, STP (must be off STP for ≥21 days prior to screening visit)
  - Felbamate (FBM), unless the patient is on FBM ≥18 months prior to screening with stable liver function and hematology laboratory tests
  - Drugs that interact with central serotonin, including imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin- (SSRI) or norepinephrine-reuptake inhibitors (SNRI), vortioxetine
  - Drugs that increase cardiovascular risk including: atomoxetine and those with noradrenergic
  - reuptake properties (NRIs, SNRIs)
  - Drugs intended to facilitate weight loss
  - Any form of marijuana, THC and derivatives (including Epidiolex®)

  If medical necessity required short-term use of one or more of these medications during the course of the study, the investigator was to contact the Medical Monitor for approval.

- **Treatment compliance**
  Patients or caregivers recorded dose, dosing frequency and IMP consumption in the patient's diary. Participants were asked to return all IMP (used, partially-used, and unused) to every study visit.

- **Rescue medications**
  The use of rescue medication was allowed and was captured on eCRFs (day, medication[s], dose[s]) and in the diary (day, timeframe associated with seizure episodes).

- **Subject completion, discontinuation, or withdrawal**
  Patients who completed the treatment period were invited to participate in an Open-label extension (OLE) study (Study 1503) under a separate protocol and continue receiving (or start taking) FEN. Patients who did not enter Study 1503 tapered the study drug after completion of the maintenance period. Patients in the 0.8 mg/kg/day group decreased to 0.4 mg/kg/day for 4 days, then to 0.2 mg/kg/day for 4 days, then stopped the FEN. Patients in the 0.2 mg/kg/day decreased to placebo on the first day of the taper period. A new bottle of the study drug was started for all patients at each step of the taper to preserve the blind. All patients who opted to transition to the OLE study transitioned from their blinded daily

dose (placebo, 0.2 mg/kg/day, 0.8 mg/kg/day, or 30 mg/day) to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 13, without breaking the blind.

Withdrawal criteria

- *Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC, in consultation with the IPCAB* [International Pediatric Cardiology Advisory Board], *the central cardiac reader, and the investigator believe the benefit of continued participation does not outweigh the risk.*
- *Subject is found to have entered the clinical investigation in violation of the protocol.*
- *Subject requires or starts using the use of an unacceptable or contraindicated concomitant medication.*
- *Subject's condition changes after entering the clinical investigation so that the subject no longer meets the inclusion criteria or develops any of the exclusion criteria.*
- *Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.*
- *Subject experiences an AE that warrants withdrawal from the clinical investigation.*
- *Clinically significant worsening of seizures, judged by investigator or subject/ caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening.*
- *An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).*
- *It is the investigator's opinion that it is not in the subject's best interest to continue in the study.*
- *Subject is found to be pregnant while on study.*

All information, including the reason for withdrawal from the study, was to be recorded in the pertinent eCRF. (1501 Protocol, p. 40)

Reviewer's comment: The specified criteria for completion, discontinuation, or withdrawal, as well as the statistical methods to address missing data in the case of discontinuation/withdrawal, appear reasonable.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was used for Study 1 was *"the change in the mean convulsive seizure frequency (MCSF) per 28 days between the Baseline and T+M periods"* in the 0.8 mg/kg/day group. *The MCSF will be calculated from all available data collected during the Baseline or T+M Periods*. Convulsive seizures were defined in the protocol as generalized tonic-clonic, tonic, clonic, tonic-atonic, hemiclonic, and focal seizures with an observable motor component. Nonconvulsive seizures included myoclonic, absence, atypical absence, or atonic

seizures, and focal seizures without an observable motor component. This efficacy endpoint was identical to that specified in the protocols of Studies 1501 and 1502.

The primary efficacy endpoint was not assessed at one specific time but was rather a measure of change in seizure frequency over the entire treatment period, which included the 2-week titration period and the 12-week maintenance period.

Patients or caregivers were to record the number and type of convulsive seizures and non-convulsive seizures each day from screening until completion of dosing using an electronic seizure diary. Seizure frequency by type and duration (<2 minutes, 2-10 minutes, >10 minutes) will also be recorded daily by the parent/caregiver.

Seizure types in the trial were as follows:

A: Hemiclonic (note lateralization – right body, left body, or independent right and left)
B: Focal with or without Retained Awareness
C: Secondarily Generalized Tonic Clonic (evolving to bilateral convulsive seizure from focal seizure)
D: Generalized Tonic Clonic Convulsion
E: Absence or Atypical Absence
F: Myoclonic
G: Tonic
H: Atonic
I: Clonic
J: Tonic/Atonic (cannot differentiate)
K: Infantile Spasms (if under 3 years of age)
L: Epileptic Spasms (if 3 years of age and older)
O: Other

Reviewer's comment: The primary endpoint used in Study 1 (percentage change from baseline in seizure frequency) is the most common efficacy endpoint AED treatment trials, although the outcome variable may differ depending on the underlying type of epilepsy. For example, in a study evaluating a drug intended to treat partial onset seizures (POS), the primary efficacy endpoint would likely be percentage change from baseline in frequency of POS. Patients with DS have multiple seizure types, with seizures ranging in severity from GTC seizures to atypical absence seizures, so careful definition of the primary outcome variable was important. The Applicant separated the seizure types into two broad categories: convulsive and non-convulsive seizures. These definitions were discussed with FDA prior to study commencement. Because convulsive seizures are the most disabling and most likely to lead to patient injury, efficacy of FEN in DS was measured by reduction in convulsive seizure frequency.

Assessment over both the titration and maintenance periods is standard in epilepsy drug treatment trials rather than over the maintenance period only, as patients may withdraw

during titration due to lack of efficacy. Capturing these patients is important, because withdrawals due to lack of efficacy may lead to unbalanced results.

Secondary Efficacy Endpoints

Key Secondary Endpoints

- *Treatment Responder Rate*
  Proportion of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline during the treatment period.

  Reviewer's comment: The 50% responder rate is a frequently reported outcome measure in clinical epilepsy treatment trials. It is often preferred by European drug regulatory agencies. It is related closely to change in seizure frequency.

- *Longest Interval Between Convulsive Seizures*
  The longest interval between convulsive seizures, calculated over the entire T+M period, is derived as the maximum of the number of days between consecutive convulsive seizures.

  Reviewer's comment: The longest interval between convulsive seizures is not an outcome measure used often in AED treatment trials; however, it may provide clinically meaningful information on duration of time between the most disabling seizures experienced by patients with DS. As with the 50% responder analysis, it is not completely independent of the primary efficacy outcome.

Other Secondary Efficacy Endpoints

A large number of secondary efficacy endpoints were evaluated in Study 1. There was significant overlap in these outcome measures, and only a select number of secondary endpoints will be discussed.

- Non-convulsive seizures
- Total seizures
- Responder Analyses (≥25 or ≥75% Reduction from Baseline)
- Clinical Global Impression of Improvement
- Status Epilepticus
- Quality of Life in Childhood Epilepsy
- Use of Rescue Medication

Secondary endpoints of particular clinical interest are discussed below.

- *Non-Convulsive Seizures*
  Non-convulsive seizures were collected, summarized, and analyzed. Patients with no non-convulsive seizures during the baseline period were excluded from the analysis. The percentage change from baseline in total nonconvulsive seizure frequency during the treatment period was calculated for each treatment group for the entire treatment period and compared between groups.

Reviewer's comment: Although this was not prespecified as a key secondary efficacy endpoint, it is a clinically important secondary endpoint.

While generally less severe and less likely to lead to injury than convulsive seizures, nonconvulsive seizures can be significantly disabling (especially POS). It is possible that a drug might reduce the number of convulsive seizures but increase the number or severity of nonconvulsive seizures in patients with multiple seizure types, such as those with DS. Increased severity or frequency of nonconvulsive seizures would be a significant adverse effect of the drug and has been reported in patients with SCN1A gene mutation who were taking AEDs that impact the sodium channel (e.g., carbamazepine, oxcarbazepine, or phenytoin). Primarily for this reason, the frequency of nonconvulsive seizures is an important secondary outcome measure.

- *Number of Convulsive Seizure Free Days*
  A convulsive seizure free day was defined as a day for which diary data are available and no convulsive seizures were reported. The total number of convulsive seizure free days was summed for the entire T+M period and similarly for the Baseline period.

- *Responder Analyses: Proportion with ≥25 or ≥75% Reduction from Baseline in Convulsive Seizure Frequency*
  Proportion of patients with a ≥25% or ≥75% reduction in convulsive seizures from baseline during the treatment period.

- *Clinical Global Impression Improvement (CGI-I)*
  The overall level of improvement due to treatment was assessed via CGI-! (parent/ caregiver and investigator) at baseline and weeks 2, 6, 10, and 14. The 7-point scale is as follows: "Very Much Improved" (1); "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse" (7). The CGI-I response/score, recorded at each visit, was summarized, on both a categorical and continuous scale, by treatment group and compared to baseline.

Safety Assessments:

- Adverse events (AEs), serious adverse events (SAEs),
- Physical and neurological examinations
- Vital signs, laboratory safety parameters, physical examination parameters

- ECGs and ECHOs
- Columbia-Suicide Severity Rating Scale (C-SSRS), Tanner staging
- Cognitive function (cognitive function was assessed using the age-appropriate versions of the Behavior Rating Index for Executive Function Scale [BRIEF])

Reviewer's comment: The planned safety assessments are acceptable.

Statistical Analysis Plan

Analysis populations

- Safety Population: all randomized patients who receive at least one dose of FEN or placebo. Safety will be analyzed according to the treatment actually received.
- Modified Intent-to-Treat (mITT) Population: all randomized patients who receive at least one dose of FEN or placebo and for whom at least one week of diary data are available. Patients will be analyzed according to the treatment group to which they were randomized. The primary comparison of FEN 0.8 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

Primary efficacy analysis

The primary endpoint is the change in the mean convulsive seizure frequency (MCSF) per 28 days between the Baseline and T+M periods. It *"will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (three levels) and age group (< 6 years, ≥6 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group using a two-sided test at the α=0.05 level of significance."* As the ANCOVA relies on the assumption of normality, the Applicant also planned to analyze the primary efficacy endpoint using a nonparametric approach such as the van Elteren test. Sensitivity analyses of change in doses or type of concomitant drugs will also be performed.

Key Secondary Efficacy Analyses

- *MCSF for 0.2 mg/kg/day vs. Placebo*
  The MCSF during the T+M period will be analyzed and compared between the FEN 0.2 mg/kg/day group and the placebo group using the same methods employed for the primary analysis.

- *Proportion with ≥50% Reduction from Baseline in Convulsive Seizure Frequency*
  Patients with a percent reduction in convulsive seizures of ≥50% from baseline will be identified and the proportion within the 0.8 mg/kg/day group will be compared to that of the placebo group. Similarly, the proportion of subjects in the ZX008 0.2 mg/kg/day group who have a reduction in convulsive frequency of ≥50% will be compared to the analogous proportion in the placebo group. The comparison between groups will be made using a logistic regression model with a categorical response variable and age group.

- *Longest Interval Between Convulsive Seizures*
  The longest interval between convulsive seizures will be calculated for each patient over the entire treatment period as specified by the Applicant: *If a subject has two consecutive days of missing diary data, the current seizure-free interval 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. [In that case, for purpose of calculation of this variable, all intervening days, after the 2nd day, with missing diary data, will be assumed to have a convulsive seizure occurrence, until the first available date with non missing diary data.]*

  …The median time of the longest convulsive seizure-free interval will be presented. Additional summary statistics will be presented, including mean, minimum, maximum, the 25th and 75th percentiles, 95% confidence intervals on the difference in medians between groups (Hodges-Lehman estimator).

Secondary Efficacy Analyses

- *Number of Convulsive Seizure Free Days*
  The total number of convulsive seizure free days will be summed for the baseline and T+M periods and will be analyzed with a similar approach to the primary efficacy endpoint.

- *Responder Analyses: Proportion of Patients with ≥25% or ≥75% Reduction from Baseline in Convulsive Seizure Frequency*
  A response curve will be generated for the mITT population. This graph will plot the % of subjects (y-axis) against percentage reduction in seizure frequency per 28 days in the T+M period (x-axis). The horizontal axis will be the % reduction, and the vertical axis will be the % of subjects achieving ≥ that % reduction. In the graph, subjects experiencing an increase or no decrease in seizure frequency (i.e., ≤0 % reduction) will be regarded as having a 0% reduction in seizure frequency.
  - *The proportion achieving a ≥25% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same method employed for the ≥50% reduction from baseline endpoint.*
  - *The proportion achieving a ≥75% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same method employed for the ≥50% reduction from baseline endpoint.*

Safety Analyses

- Assessment of differences in incidence, type and severity of AEs, Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, ECG, Echocardiograms, laboratory safety parameters, physical examination parameters, and Tanner staging of patients taking FEN compared with placebo.
- Cardiovascular safety will be presented in a separate safety analysis
- All safety summaries will be based on the SAF Population.

Protocol Amendments

There were 3 protocol amendments for Studies 1501 and 1502. Table 5 summarizes important modifications to the protocol.

Table 5: Summary of Major Protocol Amendments, Studies 1501 and 1502

Amendment Number	Date	Major Changes
1	18 DEC 2015	• Clarified maximum dose is 30 mg/day • Moved the BRIEF-P description from the efficacy section to the safety section • Clarified the transition dosing algorithm • Clarified randomization inclusion criteria, post-treatment cardiac follow-up, and AESI with regard to valve regurgitation seen on ECHO. • Clarified that the central cardiac reader will provide consultation to the IDSMC when a subject may be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension • Clarified expedited reporting of cardiac events other than SAEs • Added section on grading of and follow-up for ECHO findings.
2	18 JAN 2016	• Updated statistical analysis section to be consistent with the separate statistical analysis plan • Removed the following statement: "If any test fails to achieve significance at the α=0.05 level, then no test lower in the hierarchy can achieve statistical significance" from the statistical analysis section of the protocol • Changed assessment of cognition for patients ≥5 years of age from QOLCE to BRIEF, so that all study participants are now being assessed for cognition using the BRIEF. The description of the BRIEF was moved from the efficacy section to the safety section. • Clarified when subjects must be discontinued from the study • Clarified that the investigator may discontinue a subject from the study in the case of a medical emergency • Added statistical information regarding sensitivity analyses for concomitant AED medication changes during the study
3	31 OCT 2016	• Removed atonic seizures and added tonic-atonic from the types of convulsive seizures in Inclusion Criterion #5. • Clarify study days of Screening during the Baseline Period and the timing of assessments in that period. • Clarified the safety objective

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that Study 1 was conducted in in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. The Applicant additionally stated that informed consent and assent, if possible, were obtained prior to carrying out any study procedures. The informed consent forms (ICF), protocol, and

amendments for this trial were submitted to and approved by the IRB or independent ethics committee (IEC) at each participating trial site.

Financial Disclosure

In the financial disclosure summary, the Applicant identified 1 investigator with disclosable financial interests, which was a proprietary interest in fenfluramine. The Applicant states *"To minimize any potential bias, Study 1 was conducted as a randomized, double-blind, parallel group, placebo-controlled trial. In addition, (b) (6) was only allowed to enroll a maximum of (b) (6) subjects from his study site."*

Reviewer's comment: The methods used to mitigate any potential bias of Dr (b) (6) are acceptable. Of note, removal of Dr. (b) (6) site from the primary efficacy analysis did not change the outcome. Therefore, at the time of this review, it does not appear that Dr. (b) (6) proprietary interest in fenfluramine influenced the outcome of Study 1.

Patient Disposition

The first subject was enrolled into Study 1 on 15 JAN 2016, and the date of the last patient's last visit was 14 AUG 2017. A total of 173 patients were screened for participation in Study 1, 54 of whom were screen failures; 119 were randomized in a 1:1:1 ratio to placebo (n=40), FEN 0.2 mg (n=39), and FEN 0.8 mg (n=40). There are differences between the Applicant's and FDA's disposition analyses with respect to total number of patients who discontinued early and for the reasons adjudicated. These differences are summarized below.

As seen in Table 6 below, the majority of patients completed the study (109/119, 91.6%). All patients in the 0.2 mg/kg/day group completed the study, while 36 (90%) and 34 (85%) patients in the placebo and FEN 0.8 mg/kg/day groups, respectively, completed the study. Two of the placebo patients terminated from the study early did so due to adverse events (5.0%), and one because of lack of efficacy (2.5%). Reasons for early termination for the 6 patients in the FEN 0.8 mg/kg/day group were AEs in 5 patients (12.5%), and withdrawal by parent/guardian in 1 patient (2.5%). Of note, 3 of the patients who exited early transitioned to the OLE study (placebo: n=1; 0.8 mg/kg/day: n=2). All of the patients who exited early did so during the maintenance period.

One patient (Subj (b) (6), placebo group) was considered by the Applicant to have both completed the study and discontinued early due to "Withdrawal by Subject". When the patient narrative and case report forms were reviewed, there had been an email on 30 JAN 2017 from the site to the Medical Monitor stating that the *"parents want to terminate the study as seizure rate increased and patient status dramatically decreased (since 20-Dec-2016)."* Correspondence from the site to the CRA on 31 JAN 2017 noted that the parents wanted to change the background AEDs so early transition to the OLE study was not an option. When the exposure as collected dataset was analyzed (adec.xpt), Subj (b) (6) was reported to not have taken any study drug after 30 JAN 2017, which is consistent with the date in the

narrative. Because the patient had experienced increased seizures prior to stopping the study drug, this patient is deemed to have discontinued early due to adverse event, rather than completed the study or discontinued due to "Withdrawal by Subject".

Subj (b) (6) (placebo) was coded as "Withdrawal by Subject"; however, review of the narrative and CRFs supplied by the Applicant note that the patient experienced increased seizures, although this was not captured as an AE in the dataset. The increased seizures required initiation of a new antiseizure drug (phenobarbital), leading to early termination from Study 1. Therefore, this patient's reason for discontinuation has been revised to "Adverse Event", even though there is no concurrent AE in the adae.xpt dataset.

Table 6: Disposition Events by Arm for Exposed Patients, Study 1

Disposition Event	Placebo (N=40)	FEN 0.2 mg/kg/day (N=39)	FEN 0.8 mg/kg/day (N=40)	Total (N=119)
Completed	36 (90.0)	39 (100.0)	34 (85.0)	109 (91.6)
Adverse Event	2 (5.0)	0	5 (12.5)	7 (5.9)
Lack of Efficacy	1 (2.5)	0	0	1 (0.8)
Withdrawal by Subject	1 (2.5)	0	1 (2.5)	2 (1.7)

Source: OCS Analysis Studio, Custom Table Builder. Columns - Dataset: Demographics; Filter: SAFFL = 'Y'. Table Section 1 - Dataset: Disposition; Filter: EPOCH = 'MAINTENANCE' or 'TITRATION'. Revised by clinical reviewer.

Protocol Violations/Deviations

Overall, 33 patients had a total of 38 major protocol violations, 9 (22.5%) in the placebo group, 12 (30.8%) in the FEN 0.2 mg/kg/day group and 12 (30.0%) in the FEN 0.8 mg/kg/day group (Table 7). Major protocol deviation related to inclusion/exclusion criteria were the most frequent type, occurring in 3 (7.5%), 2 (5.1%), and 4 (10.0%) patients in the placebo, 0.2, and 0.8 mg/kg/day groups, respectively and are summarized below. Five major protocol violations occurred related to administration of study drug: 2 (5.0%) in the placebo group and 3 (7.7%) in the 0.2 mg/kg/day group. The dose administration major protocol violations in the 0.2 mg/kg/day group occurred during the Transition period between Study 1 and the open-label extension. No patients were removed from the ITT analyses for protocol deviations.

Table 7: Protocol Violations, Study 1

	Placebo (N=40) n (%)	ZX008 0.2 mg (N=39) n (%)	ZX008 0.8 mg (N=40) n (%)
Any major protocol violation	**9 (22.5)**	**12 (30.8)**	**12 (30.0)**
Concomitant treatment deviations	0 (0.0)	0 (0.0)	2 (5.0)
Inclusion/exclusion criteria deviations	3 (7.5)	2 (5.1)	4 (10.0)
Informed consent deviations	3 (7.5)	3 (7.7)	1 (2.5)
Investigational product deviations	2 (5.0)	3 (7.7)	0 (0.0)

	Placebo (N=40) n (%)	ZX008 0.2 mg (N=39) n (%)	ZX008 0.8 mg (N=40) n (%)
Laboratory deviations	0 (0.0)	2 (5.1)	0 (0.0)
Procedures/tests/assessments deviations	0 (0.0)	2 (5.1)	5 (12.5)
Randomization criteria deviations	0 (0.0)	0 (0.0)	2 (5.0)
Safety reporting deviations	0 (0.0)	1 (2.6)	0 (0.0)
Visit schedule deviations	1 (2.5)	0 (0.0)	1 (2.5)

Source: ADDV (JMP, verified)

Subject (b) (6) (placebo): The patient's screening ECHO was retroactively determined to show trace mitral regurgitation (MR) by the central reader. This finding was identified after the patient's Visit 12 ECHO showed trace MR and the central echo reader performed a second review of patient's prior ECHOs. These findings were reviewed with the Applicant, echocardiogram reader, and investigator via teleconference and a Risk Benefit Analysis was performed by the investigator and provided to the Applicant.

Subject (b) (6) (placebo): The patient was randomized without having a second screening echocardiogram. The results of the original screening ECHO were ambiguous, and a repeat echocardiogram was to be performed before randomization. However, the patient was randomized prior to obtaining this study. The repeat echocardiogram was about 1 month after randomization with no abnormal findings.

Subject (b) (6) (placebo): The patient's dose of valproate was decreased within 2 weeks of the Screening Visit from 750 mg to 600 mg, and the patient had received risperidone until 2 days prior to the Screening Visit.

Subject (b) (6) (0.2 mg/kg/day) experienced their initial seizure at 16 months. Inclusion Criterion 3 requires the first seizure by 12 months of age. This case was reviewed and approved by the independent Epilepsy Study Consortium and the Applicant.

Subject (b) (6) (0.2 mg/kg/day) experienced 5 convulsive seizures during baseline, which did not meet the protocol randomization criteria (≥ 6 convulsive seizures during the 6-week Baseline period). The patient was re-screened without obtaining approval from the medical monitor for re-screening. Upon re-screening, the patient met the randomization criteria and was permitted to remain in the study.

Subject (b) (6) (0.8 mg/kg/day) had their dose of valproate increased from 240 mg to 320 mg one day after the Screening Visit to treat an adverse event of increased seizures. The Screening period was extended to ensure at least 6 weeks of stable baseline prior to the randomization since all other criteria were met.

Subjects (b) (6), and (b) (6) (all 0.8 mg/kg/day) were randomized before receiving confirmation from the central reader that the echocardiogram results were without abnormal findings.

As noted in Dr. Grandinetti's review, a number of protocol violations were identified during the inspections of two study sites from Study 1.

- Site 0107 (Tucson, AZ): 4 patients were screened and enrolled into Study 1 from Site 0107. Twenty-three (23) protocol deviations were identified in the source records by the clinical investigator that were not reported to FDA. The most significant unreported protocol deviation from this site occurred in Subject (b) (6) (0.2 mg/kg/day treatment arm). Site personnel entered the patient's weight into the IVR/IWR system in pounds (116.8 lbs), although the system required the weight to be entered in kilograms. This patient should have received a dose of 12 mg/day at Visit 8 through Visit 12. Instead, he received the maximum dose of 30 mg/day (over two times the correct dose). An IR was sent to the Applicant on 2 MAR 2020 requesting a listing of all unreported dosing errors for both pivotal trials. This dosing error was not included in the Applicant's 13 MAR 2020 response.
- Site #0701 (Denmark): 9 patients were screened, 7 enrolled, and 6 completed the study (1 discontinued early due to lack of efficacy). A dosing error occurred in Subject (b) (6) (placebo), which was not initially reported to FDA (although it was included in the 13 MAR 2020 IR response. For this patient, site personnel entered an incorrect weight (1 kg, for a calculated dose of 0.1 mL BID) in the IVR/IWR system and corrected the weight to 17 kg. Despite the weight correction in the system, the originally calculated dose of 0.1 mL BID. The subject received an incorrect volume of study drug (placebo) for 3 days of the dose titration period.

See Section 4.1 for a discussion of the retrospective collection of seizure data and modification of the electronic diary (eDiary) data used to support the primary efficacy endpoint.

Demographic Characteristics

The baseline demographics of the patients enrolled and randomized in Study 1 (safety dataset) were similar between groups (Table 8). The mean ages were 9.3, 9.0, and 8.8 in the placebo, 0.2 mg, and 0.8 mg groups, respectively, and the distribution among the predefined age groups was also similar among the treatment groups. More than half of the patients in the placebo, FEN 0.2 mg and FEN 0.8 mg groups were from the U.S. (59%, 60.5%, and 57.5%, respectively). The rest of the patients were from Europe (38.5%, 36.9%, 37.5%), Canada (2.6%, 0, 2.5%) and Australia (0, 2.6%, 2.5%).

Table 8: Baseline Demographics (mITT Population), Study 1

Subgroup	Placebo (N = 39) n (%)	FEN 0.2 mg/kg/day (N = 38) n (%)	FEN 0.8 mg/kg/day (N = 40) n (%)	Total (N = 117) n (%)
Sex				
Female	19 (47.5)	17 (43.6)	19 (47.5)	55 (46.2)
Male	21 (52.5)	22 (56.4)	21 (52.5)	64 (53.8)
Age				
Mean	9.3	9.0	8.8	9.0
SD	5.15	4.56	4.41	4.68
Min, Max	2, 18	2, 17	2, 18	2, 18
Age Group				
<6 years	11 (28.2)	9 (23.7)	11 (27.5)	31 (26.5)
≥6 years	29 (71.8)	29 (76.3)	29 (72.5)	86 (73.5)
Race				
Native American	1 (2.6)	1 (2.6)	0 (0.0)	2 (1.7)
Asian	4 (10.3)	2 (5.3)	1 (2.5)	7 (6.0)
Missing	4 (10.2)	3 (7.9)	5 (12.5)	12 (10.2)
White	30 (76.9)	32 (84.2)	34 (85.0)	96 (82.1)
Ethnicity				
Hispanic or Latino	4 (10.3)	4 (10.5)	3 (7.5)	11 (9.4)
Missing	6 (15.4)	3 (7.9)	5 (12.5)	14 (12.0)
Not Hispanic or Latino	29 (74.4)	31 (81.6)	32 (80.0)	92 (78.6)
Region				
Canada	1 (2.6)	0 (0.0)	1 (2.5)	2 (1.7)
Europe	15 (38.5)	14 (36.9)	15 (37.5)	44 (37.6)
Other	0 (0.0)	1 (2.6)	1 (2.5)	2 (1.7)
United States	23 (59.0)	23 (60.5)	23 (57.5)	69 (59.0)
Baseline Height (m)				
Mean	1.28	1.31	1.28	1.29
SD	0.227	0.223	0.20	0.217
Median	1.28	1.33	1.30	1.30
Baseline Weight (kg)				
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
Baseline BMI (kg/m2)				
Mean	17.89	19.32	18.47	18.56
SD	3.821	5.688	3.5	4.423
Median	17.56	17.24	18.03	17.78

Source: ADSL (JMP, verified)

Other Baseline Characteristics

In general, the baseline characteristics of the patients' seizures in the three treatment groups

were reasonably similar (Table 9). All patients in all of the groups experienced convulsive seizures at baseline. The mean convulsive seizure frequency at baseline was lowest in the 0.8 mg/kg/day group (31.4) and 44.2 and 45.5 in the placebo and 0.2 mg/kg/day groups, respectively. Median baseline convulsive seizure frequency, which may be less sensitive to outliers, was greatest in the placebo group (27.33), lowest in the 0.2 mg/kg/day group (17.5) and 20.7 in the 0.8 mg/kg/day group. Baseline nonconvulsive seizure frequency was similar in all three groups.

The most commonly used concomitant AEDs were VPA [all forms] (59.7%), CLB (58.8%); TPM (25.2%); and LEV (21.8%). Differences of ≥ 10% between any of the treatment groups were noted for the following concomitant AEDs (in placebo, 0.2 mg/kg/day, 0.8 mg/kg/day groups, respectively): LEV (27.5%, 28.2%, 10.0%), ZNS (20.0%, 10.3%, 7.5%), potassium bromide (20.0%, 2.6%, 7.5%), any bromide (20.0%, 7.8%, 15.0%).

Table 9: Baseline characteristics (mITT population), Study 1

	Placebo (N = 39) n (%)	FEN 0.2 mg/kg (N = 38) n (%)	FEN 0.8 mg/kg (N = 40) n (%)	Total (N = 117) n (%)
Baseline convulsive seizure frequency				
Mean	45.47	45.29	32.9	
SD	40.691	101.054	32.332	
Median	29.44	18.14	18.67	
Min, Max	(3.3, 148.2)	(2.7, 623.5)	(6.0, 124.0)	
Baseline nonconvulsive seizure frequency				
n (%)	27 (69.2)	26 (68.4)	27 (67.5)	
Mean (SD)	148.13 (518.174)	180.03 (463.733)	292.48 (701.483)	
Number of concomitant AEDs				
n (%)	39 (100.0)	37* (97.4)	40 (100.0)	116 (99.1)
1	6 (15.0)	5 (12.8)	8 (20.0)	19 (16.0)
2	15 (37.5)	16 (41.0)	16 (40.0)	47 (39.5)
3	14 (35.0)	9 (23.1)	13 (32.5)	36 (30.3)
4	5 (12.5)	6 (15.4)	3 (7.5)	14 (11.8)
5	0 (0.0)	2 (5.1)	0 (0.0)	2 (1.7)
Concomitant AEDs				
n (%)	39 (100.0)	37* (97.4)	40 (100.0)	116 (99.1)
Any bromide	7 (17.9)	3 (7.9)	6 (15.0)	16 (13.7)
Brivaracetam	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.9)
Clobazam	21 (53.8)	23 (63.2)	24 (60.0)	68 (58.1)
Clonazepam	3 (7.5)	5 (13.2)	5 (12.5)	13 (11.1)
Diazepam	1 (2.6)	1 (2.6)	0 (0.0)	2 (1.7)
Ergenyl Chrono	1 (2.6)	0 (0.0)	1 (2.5)	2 (1.7)
Ethosuximide	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.9)
Felbamate	1 (2.6)	1 (2.6)	2 (5.0)	4 (3.4)
Lacosamide	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.9)
Lamotrigine	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.9)

	Placebo (N = 39) n (%)	FEN 0.2 mg/kg (N = 38) n (%)	FEN 0.8 mg/kg (N = 40) n (%)	Total (N = 117) n (%)
Levetiracetam	11 (28.2)	10 (26.3)	4 (10.0)	25 (21.4)
Levocarnitine	1 (2.6)	4 (10.5)	1 (2.5)	6 (5.1)
Lorazepam	3 (7.7)	0 (0.0)	1 (2.5)	4 (3.4)
Mesuximide	0 (0.0)	2 (5.3)	1 (2.5)	3 (2.5)
Midazolam	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.9)
Nitrazepam	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.9)
Perampanel	1 (2.6)	1 (2.6)	0 (0.0)	2 (1.7)
Pregabalin	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.9)
Pyridoxine	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.9)
Rufinamide	0 (0.0)	1 (2.6)	2 (5.0)	3 (2.5)
Sultiame	3 (7.7)	3 (7.7)	0 (0.0)	6 (5.1)
Topiramate	9 (23.1)	10 (26.3)	11 (27.5)	30 (25.6)
Valproate semisodium	8 (20.5)	7 (18.4)	11 (27.5)	26 (22.2)
Valproate sodium	8 (20.5)	7 (18.4)	12 (30.0)	27 (23.1)
Valproic acid	5 (12.8)	10 (26.3)	2 (5.0)	17 (14.5)
All forms of valproate	21 (53.8)	24 (61.4)	25 (62.5)	70 (59.8)
Verapamil	0 (0.0)	1 (2.6)	1 (2.5)	2 (1.7)
Zonisamide	8 (20.0)	4 (10.5)	3 (7.5)	15 (12.8)
Other Treatments for Seizures				
Ketogenic Diet	1 (2.6)	4 (10.5)	4 (10.0)	9 (7.7)
Vagal Nerve Stimulator	9 (23.0)	8 (21.1)	6 (15.0)	23 (19.7)

* One patient in the 0.2 mg/kg/day group was not on any concomitant antiepileptic drug but had a vagus nerve stimulator.
Source: ADCM (verified in JMP)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by input into the electronic diary and measurement of the residual study drug at each study visit. When compliance was measured as a percentage of assigned dose taken, most patients had ≥90% compliance in all groups: 87.5%, 87.2%, and 82.5% in the placebo, 0.2, and 0.8 mg/kg/day groups, respectively.

When the "exposure as collected" (adec.xpt) dataset for Study 1 was assessed, 14 patients overall were recorded as having missed at least one full day of study drug. Seven patients (5.9%) were reported to have missed taking their study drug completely on a single day (placebo: 2.5%, 0.2 mg/kg/day: 7.7%, 0.8 mg/kg/day: 7.5%). Two patients in the 0.2 mg/kg/day group were reported to have missed their study drug completely on 2 days (5%). One patient each missed taking their drug completely on 4 and 6 days. Three patients were recorded as having missed many days of study drug: one patient in the 0.8 mg/kg/day group missed drug on 63 days with a compliance of 30.6%. One patient in the placebo group was recorded as missing 72 days of study drug, although his compliance was measured as 62.6%. One patient in the 0.8 mg/kg/day group was recorded as missing drug completely on 30 days, with a reported compliance of 35%. Caregivers reported partial doses given to 25 patients at least once during

Study 1, with most of these instances occurring one time (13).

As seen in Table 10 below, a similar percentage of patients in each treatment group used at least one dose of rescue medication during the baseline period. During the treatment period, usage of rescue medications was numerically higher in patients randomized to placebo (77.5%) than in patients randomized to FEN 0.2 mg (59.0%), and FEN 0.8 mg (45.0%).

Table 10: Use of at least one rescue medication, Study 1

	Placebo (N=40)	FEN 0.2 mg/kg (N=39)	FEN 0.8 mg/kg (N=40)
Baseline Period	27 (67.5%)	22 (56.4%)	25 (62.5%)
T+M Period	31 (77.5%)	23 (59.0%)	18 (45.0%)

Source: Study 1, CSR, Table 14.2.7.1

Efficacy Results – Primary Endpoint

All patients who were randomized, received at least 1 dose of study drug, and had at least one post-baseline efficacy endpoint were included in the ITT analysis dataset, per their allocated treatment group: 40 in the (33.6%) the FEN 0.8 mg/kg/day group, 39 (32.8%) in the 0.2 mg/kg/day group, and 40 (33.6%) in the placebo group. The primary efficacy analyses were conducted on the mITT analysis set, which comprised a total of 117 patients; two patients (one from the placebo group and one from the FEN 0.2 mg group) were excluded from the mITT dataset, because the baseline convulsive seizure frequencies were missing or zero.

As noted above, the primary efficacy endpoint was the change from baseline in the mean convulsive seizure frequency per 28 days during the treatment (titration + maintenance) period for the 0.8 mg/kg/day group compared to placebo. Compared to the placebo group, both FEN groups had fewer seizures on average during the treatment period (Table 11). There were statistically significant differences between each FEN group (0.8 and 0.2 mg/kg/day) and the placebo group in the change from baseline in the mean convulsive seizure frequency per 28 days during the treatment period, in favor of FEN treatments ($p < 0.001$ and $p=0.043$, respectively). Based on the statistical hierarchy, the comparison between FEN 0.2 mg/kg/day and placebo on the primary endpoint is considered statistically significant because comparisons between 0.8 mg/kg/day and placebo on two key secondary endpoints had p-values < 0.05.

As per Dr. Zhang, "*Based on the least squares means from the primary analysis results, the percentage difference relative to placebo can be derived from the following formula:*

$$\frac{[\exp(LSMean(drug))-1]-[\exp(LSMean(placebo))-1]}{\exp(LSMean(placebo))-1} \times 100\%.$$

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."

Reviewer's comment: Compared with the placebo group, the FEN groups demonstrated a statistically significant reduction in convulsive seizures from baseline to the treatment period. As noted above, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint may differ based on the underlying disease. The findings are both statistically significant (p <0.001 and p=0.043) and clinically meaningful.

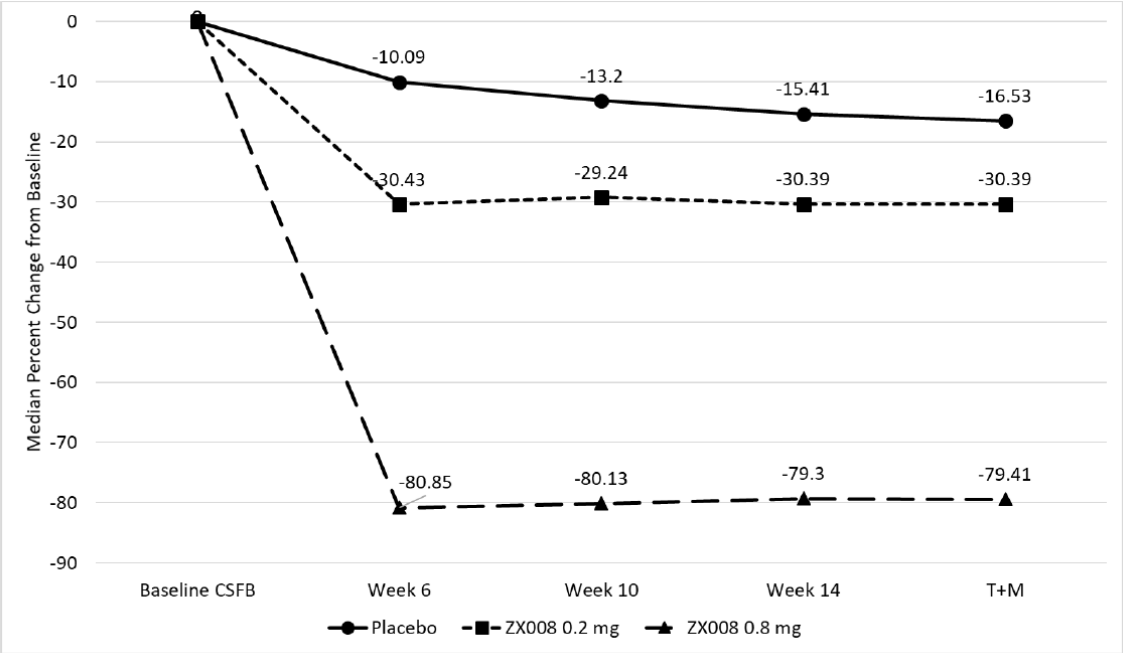
Table 11: Primary Efficacy Endpoint Results, Study 1

Convulsive Seizure Frequency per 28 days	Placebo	FEN 0.2 mg/kg/day	FEN 0.8 mg/kg/day
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 LSM	(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

Source: selected from Table 14.2.1.2_103d (IR response from Applicant, 31 MAR 2020)
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 value 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 convulsive seizure frequency as a covariate and log convulsive seizure frequency Titration + Maintenance period as response. The p-value is obtained from this ANCOVA model.

Consistent results were seen for the maintenance period and each 4-week period of the maintenance, as seen in Figure 1.

Figure 1: Median Percent Change in Convulsive Seizure Frequency During T+M, Study 1



Source: Figure 1, Applicant's response to IR 31 MAR 2020

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, race, and region. The results favored both FEN 0.8 and 0.2 mg/kg groups over placebo in almost all subgroups and are summarized in Table 12 below. Patients in the <6 years group who were randomized to 0.2 mg/kg trended worse than placebo. The small number of patients in each dose group within the <6 years subgroup makes it difficult to interpret these data.

Table 12: Subgroup Analyses of the Primary Endpoint, Study 1

Subgroup Item	Treatment	N	Baseline Mean	Treatment Mean	Least Squares Mean (SE)	Estimate of A-P (95%CI)
<6 years	Placebo	11	58.58	35.36	2.69 (0.249)	
	0.2 mg/kg	9	37.75	47.91	3.00 (0.275)	0.31 (-0.43, 1.04)
	0.8 mg/kg	11	39.74	32.42	2.17 (0.247)	-0.52 (-1.21, 0.17)
≥6 years	Placebo	28	40.32	39.38	3.17 (0.136)	
	0.2 mg/kg	29	47.63	20.50	2.58 (0.133)	-0.59 (-0.96, -0.21)
	0.8 mg/kg	29	30.35	13.36	1.84 (0.133)	-1.33 (-1.70, -0.95)
Male	Placebo	21	47.54	43.81	3.14 (0.199)	
	0.2 mg/kg	21	34.75	29.60	2.82 (0.200)	-0.33 (-0.85, 0.19)
	0.8 mg/kg	21	30.94	22.82	2.07 (0.192)	-1.08 (-1.60, -0.56)
Female	Placebo	18	43.05	31.76	2.94 (0.164)	
	0.2 mg/kg	17	58.30	23.77	2.54 (0.171)	-0.40 (-0.85, 0.05)
	0.8 mg/kg	19	35.13	13.95	1.81 (0.163)	-1.13 (-1.57, -0.69)
White	Placebo	30	49.15	43.10	3.15 (0.143)	
	0.2 mg/kg	32	49.01	27.80	2.77 (0.138)	-0.39 (-0.76, -0.01)
	0.8 mg/kg	34	36.56	21.16	2.07 (0.134)	-1.08 (-1.45, -0.72)
Non-white	Placebo	9	33.18	22.09	2.63 (0.319)	
	0.2 mg/kg	6	25.44	22.67	2.38 (0.453)	-0.25 (-1.24, 0.74)
	0.8 mg/kg	6	12.35	4.10	1.29 (0.385)	-1.33 (-2.30, -0.36)
U.S.	Placebo	23	49.82	42.17	3.24 (0.157)	
	0.2 mg/kg	23	59.52	37.62	3.14 (0.159)	-0.10 (-0.52, 0.32)
	0.8 mg/kg	23	39.56	19.57	2.23 (0.157)	-1.01 (-1.43, -0.58)
Non-U.S.	Placebo	16	39.21	32.61	2.73 (0.205)	
	0.2 mg/kg	15	23.46	10.70	1.95 (0.214)	-0.78 (-1.33, -0.23)
	0.8 mg/kg	17	23.96	17.29	1.48 (0.199)	-1.25 (-1.78, -0.72)
Clobazam (yes)	Placebo	21	59.52	45.64	3.03 (0.19)	
	0.2 mg/kg	23	55.01	28.88	2.73 (0.18)	-0.29 (-0.79, 0.20)
	0.8 mg/kg	24	27.15	19.30	2.15 (0.17)	-0.88 (-1.38, -0.37)

Subgroup Item	Treatment	N	Baseline Mean	Treatment Mean	Least Squares Mean (SE)	Estimate of A-P (95%CI)
Clobazam (no)	Placebo	18	29.07	29.62	3.07 (0.18)	
	0.2 mg/kg	15	30.38	24.09	2.64 (0.19)	-0.43 (-0.93, 0.08)
	0.8 mg/kg	16	41.61	17.57	1.63 (0.19)	-1.44 (-1.94, -0.93)
Valproate (yes)	Placebo	21	41.73	29.35	2.82 (0.18)	
	0.2 mg/kg	24	49.25	21.40	2.35 (0.17)	-0.47 (-0.96, 0.02)
	0.8 mg/kg	25	24.44	12.57	1.45 (0.17)	-0.19 (-0.61, 0.23)
Valproate (no)	Placebo	18	49.83	48.63	3.40 (0.15)	
	0.2 mg/kg	14	38.49	36.57	3.21 (0.17)	-1.37 (-1.85, -0.88)
	0.8 mg/kg	15	47.07	28.66	2.71 (0.16)	-0.69 (-1.10, -0.28)

Source: From Table 14.2.1.2_103d, Response to IR 31 MAR 2020, verified by FDA statistical reviewer

Data Quality and Integrity

See Section 4.1 for a discussion of the significant data integrity issues in Study 1.

Other issues related to the efficacy datasets identified by Dr. Zhang included incorrect application of end-of-study dates and seizures that were counted as both baseline seizures and seizures on day 1 of treatment. The efficacy dataset included seizures outside of the prespecified window for the treatment period (last day of treatment in the SAP was day 103). For example, one patient's data was derived from diary data from study day 1 to study day 131. Some seizures in 11 patients were flagged both as baseline seizures and counted as convulsive seizures on Study day 1. These issues were conveyed to the Applicant in IR's in December 2019 and revised datasets were provided.

Of note, the Applicant included incorrect SAS efficacy datasets in the original NDA submission (2/5/2019). In response to an IR regarding the inability of FDA's statisticians to replicate the efficacy results for Study 1, the Applicant stated that the penultimate datasets were included with the NDA, and corrected datasets were submitted on March 15, 2020. A refuse-to-file decision on the original NDA submission was issued because of these incorrect datasets and the need to "conduct an extensive data quality assessment to ensure the accuracy of trial results" prior to resubmitting the NDA, as well as an incomplete nonclinical package.

Efficacy Results – Secondary and other relevant endpoints

The prespecified key secondary endpoints for Study 1 were the 50% responder rate and median longest interval between convulsive seizures and are summarized in Table 13 below.

- Proportion of patients with ≥50% reduction in convulsive seizure frequency
  During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the 0.8 mg/kg/day and 0.2 mg/kg/day FEN groups (70.0% and 34.2% respectively), compared with the placebo group 7.7%). Both the 0.8 and 0.2 groups were statistically better than placebo ($p < 0.001$ and $p=0.007$, respectively).

- Median longest interval between convulsive seizures
  The longest interval between convulsive seizures is the maximum of the number of days between consecutive convulsive seizures. If two days in a row had missing seizure data, then this was considered to be a seizure-day and counted as an interruption in the interval between seizures. If there was a single day with missing diary information between two days without seizures ("no-seizure days"), this missing day was treated as also as "no-seizure" day, in the Applicant's initial analysis. When all days with missing data were considered to be days with seizures (conservative approach), then results remained statistically significant: the median longest interval between convulsive seizures were 8.0 days, 13.0 days, and 20.5 days for the placebo group, FEN 0.2

mg/kg/day group, and FEN 0.8 mg/kg/day group, respectively. Both the FEN 0.8 and 0.2 mg/kg/day groups were statistically better than the placebo group (p<0.001 and p=0.043, respectively).

Table 13: Key Secondary Endpoints Results, Study 1

	Statistic	mITT Parametric Analysis		
		Placebo	FEN 0.2 mg/kg/day	FEN 0.8 mg/kg/day
Proportion of ≥50% Responders	N	39	38	40
	Patients experienced, n(%)	3 (7.7)	13 (34.2)	28 (70)
	OR (95%CI)		6.889 (1.688, 28.122)	29.240 (7.098, 120.459)
	p-value		0.007	<0.001
Median longest interval between convulsive seizures	N	39	38	40
	Median (day)	9.0	16.5	21.5
	p-value		0.029	<0.001
Median longest interval between convulsive seizures (conservative approach)	N	39	38	40
	Median (day)	8.0	13.0	20.5
	p-value		0.043	<0.001

Source: Table B, IR response dated 31 MAR 2020

Reviewer's comment: The results of the key secondary analyses are statistically significant and generally supportive of the primary efficacy endpoint. The ≥50% reduction in convulsive seizure frequency analysis (50% responder analysis) is not independent of the primary efficacy outcome and, while helpful in defining a subset of patients who might be considered responders, does not provide information separate from the primary efficacy endpoint.

The longest interval between convulsive seizures provides information on duration of time between the most disabling seizures experienced by patients with DS. As with the 50% responder analysis, it is not completely independent of the primary efficacy outcome. It is not an outcome measure frequently used in AED treatment trials, but it is clinically meaningful and is supportive of the primary efficacy endpoint.

Other Secondary Endpoints of Clinical Interest

- Nonconvulsive Seizures
  Nonconvulsive seizures were reported during baseline in 67.5% of 0.8 mg/kg/day patients, 68.4% of 10.2mg/kg/day patients, and 69.2% of placebo patients in the mITT analysis set. Greater mean and median reductions from baseline in nonconvulsive seizure frequency during the treatment period were seen in the 0.8 mg/kg/day group, compared with the placebo group (Table 14), while there was essentially no difference in reduction between the 0.2 mg/kg/day and placebo groups.

Table 14: Change from Baseline in Nonconvulsive Seizures, Study 1

	Placebo (N=39)	FEN 0.2 mg/kg/day (N=38)	FEN 0.8 mg/kg/day (N=40)
Baseline Summary Statistics			
N	27	26	27
Mean (SD)	148.13 (518.174)	180.03 (463.733)	292.48 (701.483)
Median	18.12	22.5	32.00
Min, Max	0.7, 271.6	0.7, 2164.9	0.7, 3228.0
T+M Period Summary Statistics			
N	27	26	27
Mean (SD)	110.94 (414.177)	90.80 (216.563)	112.42 (282.768)
Median	21.91	4.39	12.41
Min, Max	0.0, 2169.8	0.0, 1035.7	0.0, 1280.6
Change from Baseline			
N	27	26	27
Mean (SD)	-37.19 (106.751)	-89.23 (348.207)	-180.06 (453.895)
Median	-3.41	-3.38	-15.76
Min, Max	-546.2, 30.6	-1767.5, 192.3	-1947.4, 0.0
Percent Change from Baseline			
N	27	26	27
Mean (SD)	-14.32 (131.615)	-24.60 (103.628)	-63.88 (32.158)
Median	-53.57	-56.80	-76.91
Min, Max	-100.0, 486.1	-100.0, 360.6	-100.0, 0.0

Source: Table 7, Response to IR dated 31 MAR 2020

Reviewer's comment: Although not pre-specified in the SAP as a hierarchical secondary efficacy endpoint for the purposes of statistical analysis, change in nonconvulsive seizures is an important endpoint from the clinical perspective, especially as a measure of safety. A general concern with epilepsy disorders in which there are frequent multiple seizure types is that a treatment may improve one or more type of seizures and worsen others. Nonconvulsive seizures, while not as disabling as convulsive seizures, still cause significant morbidity for patients with DS, although they are generally more difficult to quantify reliably in a trial setting. The analysis of median change in nonconvulsive seizure frequency favors the 0.8 mg group over placebo and shows essentially no difference between the 0.2 mg and placebo groups. This finding suggests that that FEN may have a broad antiepileptic effect in patients with DS, although a definitive conclusion cannot be drawn.

- Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom
  A higher proportion of patients in both the 0.8 mg/kg and 0.2 mg/kg FEN groups had a ≥25% reduction in convulsive seizure frequency from baseline during the treatment period compared with patients in the placebo group (90.0% and 55.3% vs. 35.9%,

respectively). 57.5% of patients in the FEN 0.8 mg/kg group achieved a ≥75% reduction in convulsive seizure frequency during the treatment period compared with 34.2% in the FEN 0.2 mg/kg group and 2.6% in the placebo group. Three patients each in the 0.8 mg (7.5%) and 0.2 mg (7.9%) groups and 0 patients in the placebo group had no convulsive seizures during the treatment period. See Table 15 below for specifics.

Table 15: Summary and Analysis of Convulsive Seizure Treatment Responders, Study 1

	Placebo (N=39)	0.2 mg/kg (N=38)	0.8 mg/kg (N=40)
≥25% Reduction			
Yes	14 (35.9%)	21 (55.3%)	36 (90.0%
Odds Ratio (95% CI) [Active/Placebo]		2.347 (0.914, 6.025)	19.237 (5.276, 70.140)
≥50% Reduction			
Yes	3 (7.7%)	13 (34.2%)	28 (70.0%)
Odds Ratio (95% CI) [Active/Placebo]		6.889 (1.688, 28.122)	29.240 (7.098, 120.459)
p-value*		0.007	<0.001
≥75% Reduction			
Yes	1 (2.6%)	8 (21.1%)	23 (57.5%)
Odds Ratio (95% CI) [Active/Placebo]		10.770 (1.231, 94.221)	81.253 (8.498, 776.879)
100% Reduction			
Yes	0 (0.0%)	3 (7.9%)	3 (7.5%)
Odds Ratio (95% CI) [Active/Placebo]			

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.
**Two separate logistic regression models that include a categorical response variable (achieved xx percentage point reduction, yes or no) as a function of treatment group (Active or placebo), age group (< 6 years1 ~ 6 years) and baseline convulsive seizure frequency were used.*
Source: Modified from Table 6, Response to IR dated 31 MAR 2020

Clinical reviewer's comment: Overall, the responder analysis favored FEN (both dose groups) over placebo. Because of the small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of FEN over placebo. The difference between the FEN groups and placebo is notable for the ≥25% and ≥75% responders and is statistically significant for the ≥50% responders. Of note is the difference between FEN and placebo with respect to 0 convulsive seizures (3 patients each in the FEN groups and 0 in the placebo group. No seizures during a prolonged treatment period is a clinically meaningful outcome, especially in this particularly refractory epilepsy syndrome.

- Patient/Caregiver Global Impression of Improvement (CGI-I)
  For the analysis of CGI-I score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. The number (%) of patients who were rated as showing improvement (had a score of "minimally improved", "much improved", or "very much improved") for the 0.8 mg, 0.2 mg, and placebo groups at the EOS visit were 26 (65.0), 22 (56.4), and 12 (30.0). As seen in Table 16 below, the treatment differences were in favor of both the 0.8 and 0.2 mg/kg/day FEN groups (OR=12.0 and OR=5.3, respectively).

Table 16: Patient/Caregiver Global Impression of Improvement (CGI-I), Study 1

Summary Description	Placebo (N=39)	ZX008 0.2 mg (N=38)	ZX008 0.8 mg (N=40)
Visit 12 Summary Statistics			
n	36	39	37
Mean (SE)	3.9 (0.19)	3.1 (0.26)	2.6 (0.27)
Median	4.0	3.0	2.0
Min, Max	1, 6	1, 6	1, 7
Number and percentage of subjects with CGI scales at Visit 12			
1= Very much improved	1 (2.5%)	8 (20.5%)	11 (27.5%)
2= Much improved	3 (7.5%)	8 (20.5%)	11 (27.5%)
3= Minimally improved	8 (20.0%)	6 (15.4%)	4 (10.0%)
4= No change	14 (35.0%)	8 (20.5%)	6 (15.0%)
5= Minimally worse	7 (17.5%)	6 (15.4%)	2 (5.0%)
6= Much worse	3 (7.5%)	3 (7.7%)	2 (5.0%)
7= Very much worse	0 (0.0%)	0 (0.0%)	1 (2.5%)
Improvement			
Improved (1,2,3)	12 (30.0%)	22 (56.4%)	26 (65.0%)
Odds Ratio vs. placebo		2.6	4.6
"Clinically Meaningful" Improvement			
Much improved or very much improved (1, 2)	4 (10.0%)	16 (41.0%)	22 (55.0%)
Odds Ratio vs. placebo		5.3	12.0

Source: Table 27, Study 1 CSR

Dose/Dose Response

See Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance period. Consistent results were seen for both doses of FEN for each of these time periods in Study 1. See also Section 7.1.5.

Additional Analyses Conducted on the Individual Trial

As noted in Section 2.X above, any one (or more) of a variety of genetic mutations in the SCN1A gene have been frequently reported in patients with a clinical diagnosis of DS. A majority (70-80%) of patients with the clinical syndrome have a mutation in the sodium channel.[6,17,18] in general, SCN1A genetic mutations (or absence of genetic mutation) have not correlated with prognosis, severity of disease, or response to AEDs in patients with DS. Even so, it is important to explore any potential differences in response to FEN based on the presence or absence of SCN1A genetic mutations. One or more mutations in the SCN1A gene were identified in most patients in the mITT population of Study 1 (95/117 [81.1%]): 31 (79.5%), 31 (81.6%), and 33 (82.5%) in the placebo, 0.2, and 0.8 mg/kg groups, respectively.

As seen in Table 17 below, there was a reduction in mean convulsive seizure frequency per 28 days vs baseline in both FEN groups compared to placebo.

Table 17: Subgroup Analysis of the Primary Endpoint by *SCN1A* status, Study 1

	Placebo		FEN 0.2 mg/kg/day		FEN 0.8 mg/kg/day	
	SCN1A+	SCN1A-	SCN1A+	SCN1A-	SCN1A+	SCN1A-
Baseline Summary Statistics						
N	31	8	31	7	33	7
Mean (SD)	47.77 (43.35)	36.55 (28.66)	46.58 (111.26)	39.54 (32.13)	32.22 (33.17)	36.26 (30.21)
Median	29.44	37.06	18.12	56.00	17.33	25.67
Min, Max	3.41, 148.2	3.33, 74.67	2.95, 623.51	2.67, 74.67	6.00, 124.00	7.41, 83.22
T+M Period Summary Statistics						
N	31	8	31	7	33	7
Mean (SD)	36.00 (37.62)	46.97 (35.21)	30.13 (41.97)	13.10 (12.85)	14.06 (20.47)	40.01 (63.09)
Median	19.80	55.56	12.57	8.47	2.95	4.53
Min, Max	2.71, 163.71	5.89, 84.00	0.00, 199.71	0.00, 37.24	0.00, 65.94	0.28, 169.93
T+M Period: Parametric Model Summary (results on a log scale) [1]						
Least Squares Mean (SE) [1]	2.92 (0.13)	3.84 (0.47)	2.79 (0.14)	2.48 (0.42)	1.87 (0.13)	2.56 (0.42)
Estimate of A-P (95% CI)[1]			-0.13 (-0.50, 0.23)	-1.36 (-2.36, -0.35)	-1.05 (-1.41, -0.69)	-1.27 (-2.28, -0.27)

SCN1A+ = patients with any reported mutation in the SCN1A gene during the trial.
SCN1A- = patients without any reported mutation in the SCN1A gene
Source: FDA statistician

Reviewer's Comments: Both FEN groups demonstrated greater reduction in mean convulsive seizure frequency from baseline compared to placebo regardless of *SCN1A* status, suggesting that presence or absence of mutations of the *SCN1A* gene are not a factor in response to FEN. As this subgroup analysis was not prespecified in the SAP, p-values are not reported.

6.2. Study 1504-C2

6.2.1. Study Design

Title

A Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome

Overview and Objective

Study 1504-C2 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of fenfluramine (ZX008) in patients with refractory seizures and Dravet syndrome who were taking concomitant stiripentol.

The objectives of this study were as follows:

- Primary: *To demonstrate that ZX008 is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults stabilized on a STP regimen based on the change in the frequency of convulsive seizures between the Baseline period and the combined Titration and Maintenance (T+M) periods in Cohort 2.*
- Key Secondary:
  To demonstrate that ZX008 is superior to placebo in the following:
  - *The proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency.*
  - *The longest convulsive seizure-free interval*
- Safety objective: *To compare the safety and tolerability of ZX008 to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight. Cognitive function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the Brief Rating Inventory Executive Function (BRIEF).*

The study protocol included a number of other secondary and exploratory objectives.

Trial Design

- **Basic Study Design**
  Study 1504-C2 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of fenfluramine conducted at 28 centers worldwide. This study was conducted to test the clinical efficacy, safety, and PK of fenfluramine oral solution in patients with seizures associated with Dravet syndrome who were taking concomitant STP. The total duration of patient participation in the study was approximately 22 weeks with duration of treatment about 16 weeks. The study consisted of a Baseline Period (6 weeks), a Treatment Period

(titration [3 weeks] plus maintenance [12 weeks]), and a Taper/Transition Period (alternatively, patients enrolled in an open label, long-term extension [LTE] study).

The general design of Study 1504-C2 was similar to other pivotal trials evaluating efficacy of AED treatments, in general, and other DS studies, in particular.

- **Trial location**
  Study 1504 was conducted in the U.S., Canada, and Europe (Great Britain, Germany, France, Netherlands, and Spain). The patient population and treatment regimen in Europe is expected to be similar to that in the U.S.

- **Choice of control group**
  The Applicant used a concurrent placebo control as the comparator group, as recommended in FDA Guidelines for the Clinical Evaluation of Antiepileptic Drugs (Adults and Children)[28]. At the time that this trial commenced, there was no approved treatment for seizures associated with DS in the U.S., comparison to placebo was deemed appropriate.

- **Diagnostic criteria**
  Patients were enrolled if they had a "documented medical history to support a clinical diagnosis of Dravet Syndrome" – a clinical diagnosis – a variety of treatment-resistant seizures that began in the first year of life (including convulsive seizures) and cognitive decline or developmental delay. Although patients were tested for genetic anomalies (most importantly SCN1A mutations), presence of such mutations were not required for inclusion in the study, which is consistent with the currently accepted clinical diagnosis of DS.

- **Key inclusion/exclusion criteria**
  Inclusion Criteria:
  1. Age between 2 and 18 years
  2. Females of childbearing potential must not be pregnant or breast-feeding and must have a negative urine pregnancy test. Patients must be willing to use medically acceptable forms of birth control, which included abstinence, while being treated on this study and for 90 days after the last dose of study drug.
  3. Have a documented history "*to support a clinical diagnosis of*" DS, with convulsive seizures not completely controlled by current AEDs.
  4. Must meet all of the following:
     a. *Onset of seizures in the first year of life in an otherwise healthy infant.*
     b. *A history of seizures that were either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.*
     c. *Initial development was normal.*
     d. *History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.*
     e. *Lack of alternative diagnosis*

[28] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071582.pdf

5. Must meet ≥ 1 of the following:
    a. *Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal developed after the first seizure type.*
    b. *Prolonged exposure to warm temperatures induced seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths, high levels of activity, and sudden temperature changes, and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.*
    c. *Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis).*
6. Must have had ≥4 convulsive seizures (i.e., tonic, clonic, tonic-clonic, tonic-atonic) per 4-week period for the past 12 weeks prior to Screening.
7. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for four weeks prior to screening and are expected to remain stable throughout the study.
8. Must be receiving a therapeutically relevant and stable dose of CLB, VPA, and STP for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
9. Agrees to a buccal swab for CYP2D6 (cytochrome P450 2D6) genotyping
10. Informed consent (and assent if possible) obtained.

Exclusion Criteria:

1. Known hypersensitivity to fenfluramine hydrochloride or any of the excipients in the study medication.
2. Pulmonary arterial hypertension.
3. Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, or stroke.
4. Current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration > 1 month.
5. At imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must have been excluded if they reported suicidal behavior in the past 6 months, as measured by the C-SSRS at Screening or Baseline, which included suicidal ideation with intent and plan (Item #5). If a subject reported suicidal ideation on Item 4 without specific plan, and the investigator felt that the subject was appropriate for the study considering the potential risks, the investigator must have documented appropriateness for inclusion, and discussed with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Current or past history of glaucoma.
7. Moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [ULN] and/or

elevated bilirubin < 2xULN) may have been entered into the study, after review and approval by the Medical Monitor in conjunction with the Sponsor, with consideration of potential cause, concomitant medications, and other risk factors.

8. Receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally acting noradrenergic agonist; or cyproheptadine.
9. Currently taking CBZ, OXC, eslicarbazepine (ESL), phenobarbital [PHB], or PHT, or had taken any of these within the past 30 days, as maintenance therapy.
10. Unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Baseline period and throughout the study.
11. Had positive results on the urine tetrahydrocannabinol (THC) Panel or the whole blood cannabidiol (CBD) at the Screening Visit.
12. Participated in another clinical trial within the past 30 days.
13. Currently receiving an investigational product.
14. Unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
15. Has a clinically significant condition, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Randomization Inclusion Criteria

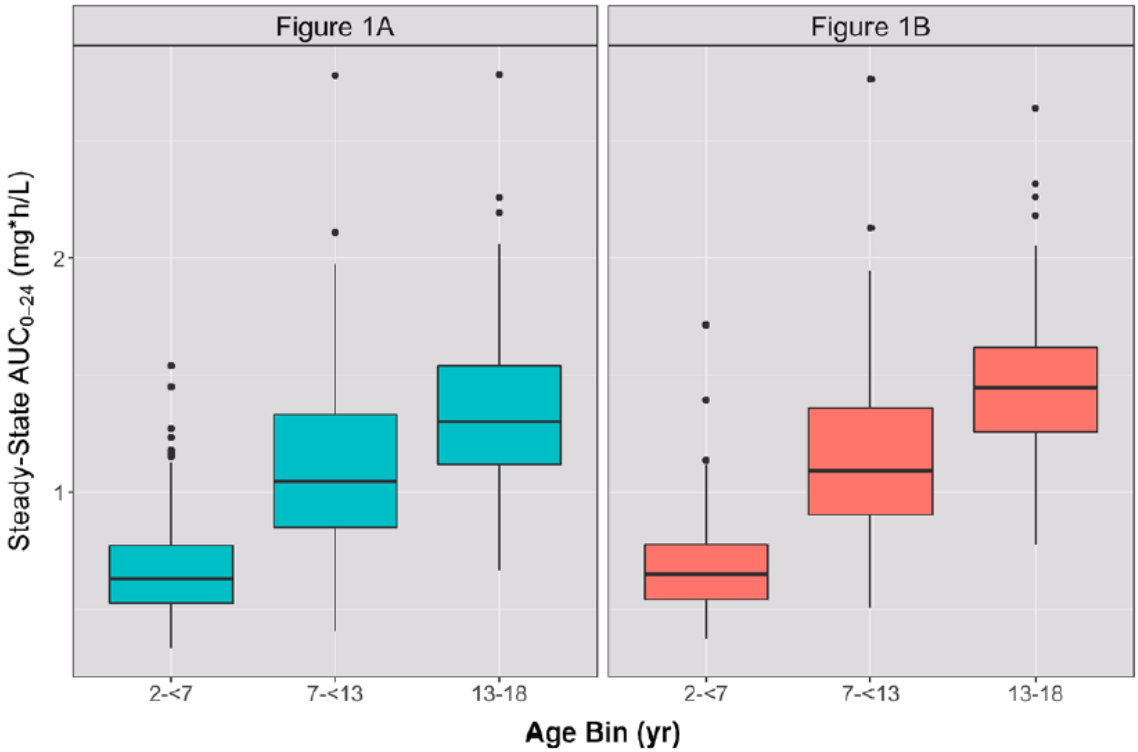
1. Approved for study inclusion by the Epilepsy Study Consortium.
2. Does not have a cardiovascular or cardiopulmonary abnormality based on screening ECHO, ECG, or physical examination, including but not limited to trace mitral or aortic valve regurgitation or signs of pulmonary hypertension, and was approved for entry by the central cardiac reader.
3. Has a stable baseline with ≥ 6 convulsive seizures during the 6-week Baseline period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks.
4. Parent/caregiver compliant with diary completion during the Baseline period, in the opinion of the investigator (e.g., at least 90% compliant).

Reviewer's comment: The eligibility criteria for Study 1504-C2 were generally similar to those in other AED treatment trials and were almost identical to those used in Study 1.

- **Dose selection**

The dosage of 0.5 mg/kg/day (maximum dose 20 mg/day) was selected based on data from Cohort 1, as well as from a completed drug-drug interaction study (DDI, Study 1505). Based on the PK data from cohort 1 and Study 1505, it was determined that the PK of 0.5 mg/kg/day in patients on concomitant STP was comparable to 0.8 mg/kg/day in patients not taking concomitant STP (Figure 2). See page 38 for the rationale of 0.8 mg/kg/day as the maximum dosing in Study 1.

Figure 2: Comparative bioavailability of FEN with and without concomitant STP (predicted steady-state exposure as a function of age), Study 1504



Source: Protocol Study 1504: Figure 1A: Fenfluramine 0.8 mg/kg/day, maximum 30 mg/day, no STP or CLB; and Figure 1B: Fenfluramine 0.5 mg/kg/day, maximum 20 mg/day, STP 1000 mg/day, CLB 10 mg/day

Reviewer's Comments: The justification for the selection of the 0.5 mg/kg/day dose of fenfluramine (maximum 20 mg/day) is based on the comparative bioavailability to the 0.8 mg/kg/day dose (single dose) and is acceptable.

- **Study treatments**
  Subjects randomized to the FEN treatment group received daily doses of FEN oral solution (2.5 mg/mL) at 0.5 mg/kg/day, divided BID. Titration schedule is summarized in Table 18 below. Patients in the placebo arm received equal volumes of placebo oral solution using an identical titration schedule.

Table 18: Titration schedule, Study 1504-C2

Randomized Group	Titration Step 1 Study Days 1-7	Titration Step 2 Study Days 8-14	Titration Step 3 Study Days 15-21
FEN 0.5 mg/kg/day	FEN 0.2 mg/kg/day	FEN 0.4 mg/kg/day	FEN 0.5 mg/kg/day
Placebo	Placebo	Placebo	Placebo

Reviewer's comment: The proposed labeling does not include a stepwise titration schedule for dosing in patients taking concomitant STP. This should be addressed.

- **Assignment to treatment**
  At the initial screening visit, a unique patient number was assigned to each patient. Patients were randomly allocated to FEN 0.5 mg/kg/day or equivalent volume of placebo using an interactive web response system (IWRS).

Reviewer's comment: Patients were randomized after completion of the 6-week baseline period, as they were required to have ≥6 convulsive seizures during this time. Patients who did not have sufficient seizures (or were non-compliant with seizure recording) during the baseline were considered screen failures. This is consistent with other AED trials.

Randomization was stratified by age group (<6 years, ≥6 years) and was performed globally.

- **Blinding**
  Once patient was randomized and received a number, the site recorded the patient's initials on the corresponding study drug labels. Each bottle contained the assigned treatment (FEN or placebo). The FEN and placebo solutions were identical. The IWRS instructed site personnel to the volume of oral solution to be administered based on that subject's weight. Dose was recalculated by the system once at the midpoint of the study.

Reviewer's comment: The described methods of blinding appear adequate. The primary endpoint of change in convulsive seizure frequency could potentially be influenced by unblinding, in that an unblinded caregiver could report seizures differently based on assumption of treatment allocation. Even so, seizure counts remain the most clinically relevant outcome measure of efficacy of a seizure treatment, and the outcome measure/endpoint is standard in AED treatment trials.

This potential for reporting bias is complicated by the retrospective reporting of seizures identified in the EMA inspection and the OSI review. See Section 4.1 for further discussion.

- **Dose modification, dose discontinuation**
  Patients were to continue on a stable dose after titration. However, in the case of a poorly tolerated dose during the maintenance period, the investigator was permitted to temporarily or permanently reduce the dose for the remainder of the study. If an unacceptable AE occurred at any time during titration, dosing was to be suspended or

amended as advised by the investigator, until the event resolved. Such dose modifications were captured in the CRFs.

See Section 13.3.1 below for the predefined echocardiographic criteria which triggered DSMC assessment for continued participation in Study 1504-C2.

- **Administrative structure**
  Investigators at 28 study centers worldwide received IRB/IEC approval to participate in this study, and 25 centers randomized patients into Study 1504-C2. Safety data were reviewed on an ongoing basis by the Applicant's Medical Monitor and by an independent Data Safety Monitoring Committee (IDSMC). An independent study consortium evaluated all patients for the DS diagnosis and verified the seizure types of screened patients.

- **Procedures and schedule**
  The following table from the study protocol summarizes the schedule of study visits, baseline period, treatment period, taper period, and follow-up period.

Table 19: Schedule of Assessments, Study 1504-C2

Study Assessments	Baseline Period[a]			Treatment (Titration + Maintenance) Period									EOS/ ET[b]	Follow -up[c]	Cardiac F/U
	Screening	2*	Random-ization	Titration Period				Maintenance Period							
Visit Number	1		3		4*	5	6	7*	8	9*	10	11*	12	13	14
Study Day	-43 to -42 or -42 to -41	-21	-1	1	8	15	22	36	50	64	78	92	106	120	3-6 mos post last dose
Informed Consent	X														
Inclusion/Exclusion Criteria	X		X												
Demographics	X														
Medical/Neurological History	X														
Epilepsy history	X														
Collect retrospective seizure diary data	X														
Prior Medication	X		X												
Physical Exam, complete	X		X										X		X
Physical Exam, abbreviated							X		X		X				X
Neurological Exam, complete	X												X		
Neurological Exam, abbreviated			X				X								
Vital signs	X		X				X		X		X		X		
Weight, Height, BMI	X		X				X		X		X		X		
12-lead ECG	X		X										X		X
Doppler ECHO	X										X[d]				X
Urine pregnancy test	X[e]		X[e]				X[e]		X[e]		X[e]		X[e]		
Clinical laboratory eval (hematology/ clinical chemistry/ UA, etc.	X		X				X		X		X		X		

Study Assessments	Baseline Period[a]			Treatment (Titration + Maintenance) Period									EOS/ ET[b]	Follow -up[c]	Cardiac F/U
	Screening	2*	Random-ization	Titration Period				Maintenance Period							
Visit Number	**1**		**3**		**4***	**5**	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13**	**14**
Plasma sample for FEN PK									4X[f]						
Plasma sample for background AEDs			X				X						X[g]		
Urine THC Panel	X		X				X		X		X		X		
Tanner Staging (>7 yrs old)			X										X		
Subject Diary	D	R	C/R/D		R	C/R/D	C/R/D	R	C/R/D	R	C/R/D	R	C/R/Dh	C/R	
Epilepsy genotype panel	X														
Study Medication			D		R[i]	C/R/D	C/R/D	R	C/R/D	R	C/R/D	R	C/R/Dh	C/R	
C-SSRS	X		X				X		X		X		X		
CGI-I (parent/ caregiver)						X	X		X		X		X		
CGI-I (investigator)						X	X		X		X		X		
Sleep quality & mealtime behavior questions			X						X				X		
Karolinska Sleepiness Scale			X						X				X		
BRIEF			X						X				X		
QOLCE			X						X				X		
PEDsQL Generic Core Scale			X						X				X		
PedsQL Family Impact Module			X										X		
EQ-5D-5L (QoL of parent/ caregiver)			X						X				X		
Randomize subject			X												
First Day of Study Drug Administration				X[j]											

Study Assessments	Baseline Period[a]			Treatment (Titration + Maintenance) Period									EOS/ ET[b]	Follow -up[c]	Cardiac F/U
	Screening	2*	Random-ization	Titration Period				Maintenance Period							
Visit Number	**1**		**3**		**4***	**5**	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13**	**14**
Daily Diary Completion		X													
Concomitant Medication					X										
Adverse events		X													
AESI		X													X

Source: modified from Table 2, Protocol, Study 1504
*Phone visit
Abbreviations: AED = antiepileptic drug; AESI = Adverse events of special interest; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Function; BRIEF-P = BRIEF scale preschool; C = Collect; D = Dispense; ECG = electrocardiogram; EOS = end of study; ET = early termination; EQ-5D- 5L = standardized measure of health status; PedsQL = Pediatric Quality of Life Inventory; QoL = quality of life; QOLCE = Quality of Life in Childhood Epilepsy; R = Review.

- **Concurrent medications**
  Patients had to be on at least one AED at a stable dose during the trial. All non-pharmacological therapies for epilepsy (e.g., ketogenic diet, VNS) also had to be stable for four weeks prior to screening and remain so throughout the duration of the study.

  Any medication, other than study drug, taken during the study was to be recorded on the appropriate Case Report Form (CRF).

  Prohibited therapies during the study period were as follows:
  - AEDs: PHT, CBZ, OXC, ESL, retigabine/ezogabine, STP (must be off STP for ≥21 days prior to screening visit)
  - Felbamate (FBM), unless the patient is on FBM ≥18 months prior to screening with stable liver function and hematology laboratory tests
  - Drugs that interact with central serotonin, including imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin- (SSRI) or norepinephrine-reuptake inhibitors (SNRI), vortioxetine
  - Drugs that increase cardiovascular risk including: atomoxetine and those with noradrenergic
  - reuptake properties (NRIs, SNRIs)
  - Drugs intended to facilitate weight loss
  - Any form of marijuana, THC and derivatives (including Epidiolex®)

  If medical necessity required short-term use of one or more of these medications during the course of the study, the investigator was to contact the Medical Monitor for approval.

- **Treatment compliance**
  Patients or caregivers recorded dose, dosing frequency and study drug consumption in the patient's diary. Participants were asked to return all study drug(used, partially-used, and unused) to every study visit.

- **Rescue medications**
  The use of rescue medication was allowed and was captured on eCRFs (day, medication[s], dose[s]) and in the diary (day, timeframe associated with seizure episodes).

- **Subject completion, discontinuation, or withdrawal**
  Patients who completed the treatment period were invited to participate in an Open-label extension (OLE) study (Study 1503) under a separate protocol and continue receiving (or start taking) FEN. Patients who did not enter Study 1503 tapered study drug after completion of the maintenance period. All patients in the FEN group decreased to 0.4 mg/kg/day for 4 days, then to 0.2 mg/kg/day for 4 days, then stopped the drug. A new bottle of study drug was started for all patients at each step of the taper to preserve the blind. All patients who opted to transition to the OLE study transitioned from their blinded daily dose to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 13, without breaking the blind.

Withdrawal criteria

- *Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC, in consultation with the IPCAB, the central cardiac reader, and the investigator believe the benefit of continued participation does not outweigh the risk.*
- *Subject is found to have entered the clinical investigation in violation of the protocol.*
- *Subject requires or starts using the use of an unacceptable or contraindicated concomitant medication.*
- *Subject's condition changes after entering the clinical investigation so that the subject no longer meets the inclusion criteria or develops any of the exclusion criteria.*
- *Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.*
- *Subject experiences an AE that warrants withdrawal from the clinical investigation.*
- *Clinically significant worsening of seizures, judged by investigator or subject/ caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening.*
- *An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).*
- *It is the investigator's opinion that it is not in the subject's best interest to continue in the study.*
- *Subject is found to be pregnant while on study.*

Discontinuation criteria for ECHO findings were identical to those used in Study 1. See Section 13.3.1.

All information, including the reason for withdrawal from the study, was to be recorded in the pertinent eCRF.

Reviewer's comment: The specified criteria for completion, discontinuation, or withdrawal, as well as the statistical methods to address missing data in the case of discontinuation/withdrawal, appear reasonable.

Study Endpoints

In general, methods used to analyze the efficacy endpoints in Study 1504-C2 were the same as those used to analyze the efficacy endpoints in Study 1, although comparison with only dose was performed for Study 1504-C2.

Primary Efficacy Endpoint

The primary efficacy endpoint was used for Study 1504 was *"the change in the mean convulsive seizure frequency (MCSF) per 28 days between the Baseline and T+M periods"* in the 0.8

mg/kg/day group. *The MCSF will be calculated from all available data collected during the Baseline or T+M Periods*. This efficacy endpoint was identical to that specified in the protocols of Studies 1501 and 1502.

The primary efficacy endpoint was not assessed at one specific time but was rather a measure of change in seizure frequency over the entire treatment period, which included the 2-week titration period and the 12-week maintenance period.

Patients or caregivers were to record the number and type of convulsive seizures (tonic, clonic, tonic–clonic, or atonic) and non-convulsive seizures (myoclonic, partial, or absence) each day from screening until completion of dosing using an electronic seizure diary.

Reviewer's comment: The primary endpoint used in Study 1504-C2 was the same as that used in Study 1 (percentage change from baseline in seizure frequency). See pages 44-46 for discussion of clinical relevance of the primary efficacy endpoint.

Secondary Efficacy Endpoints

Key Secondary Endpoints

- *Treatment Responder Rate*
  Proportion of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline during the treatment period.

- *Longest Interval Between Convulsive Seizures*
  The longest interval between convulsive seizures will be calculated over the entire T+M period. This is derived as the maximum of the number of days between consecutive convulsive seizures.

- *Proportion of Patients with 0 or 1 Convulsive Seizures*
  The proportion of patients with either no or 1 convulsive seizure will be identified, and descriptive statistics will be presented by treatment group.

  Reviewer's comment: Prolonged periods of no seizures is generally considered to be the ultimate goal of treatment with AEDs. Seizures in patients with Dravet syndrome are particularly refractory to treatment, and patients with DS rarely achieve prolonged periods without seizures even when taking multiple seizure drugs; therefore, the proportion of patients who have no convulsive seizures during the analysis period (not 1 or fewer seizures) is of clinical interest.

Statistical Analysis Plan

Analysis populations

- Safety Population: all randomized patients who receive at least one dose of FEN or

placebo. Safety will be analyzed according to the treatment actually received.

- Modified Intent-to-Treat (mITT) Population: all randomized patients who receive at least one dose of FEN or placebo and for whom at least one week of diary data are available. Patients will be analyzed according to the treatment group to which they were randomized. The primary comparison of FEN 0.5 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

Primary efficacy endpoint

As noted above, the primary efficacy endpoint is the change in the MCSF per 28 days between baseline and T+M periods. The SAP for Study 1504-C2 states that the convulsive seizure frequency will be calculated for each patient from all available data collected during the baseline and treatment periods, and the MCSF for each treatment group will be calculated for the baseline period and T+M period.

The primary analysis will compare the ZX008 0.5 mg/kg/day group to the placebo group using a two-sided test at $\alpha = 0.05$ level of significance. The primary endpoint (CSFT+M) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (ZX008 or Placebo) and age group (< 6 years, ≥6 years) as classification factors, log baseline frequency (CSFB) as a covariate in the model, and log CSFT+M as response. Treatment group means and the difference from placebo will be estimated with least squares means from the analysis model along with 95% confidence intervals and associated 2-sided p-values. Estimated treatment group means and CI endpoints will be exponentiated for presentation. (Study 1504-C2, SAP, pgs. 30-31)

Key Secondary Efficacy Analyses

- *Proportion with ≥50% Reduction from Baseline in Convulsive Seizure Frequency*
  Patients with a percent reduction in convulsive seizures of ≥50% from baseline will be identified and the proportion within the FEN group will be compared to that of the placebo group. The comparison between groups will be made using a logistic regression model with a categorical response variable and age group.

- *Longest Interval Between Convulsive Seizures*
  The longest interval between convulsive seizures will be calculated for each patient over the entire treatment period as specified by the Applicant and analyzed identically to the method used in Study 1, although for a single FEN dose group.

- *Proportion of subjects with 0 or 1 Convulsive Seizures*
  The proportion of patients with either no or 1 convulsive seizure will be identified, and descriptive statistics will be presented by treatment group. The SAP specifies that a Fisher's exact test will compare the proportion of patients with 0 convulsive seizures, as well those with ≤1 convulsive seizures, in the FEN 0.5 mg/kg/day to the placebo group. Of note, this endpoint was not included in the testing hierarchy.

Other Secondary Efficacy Analyses

- *Number of Convulsive Seizure Free Days*

The total number of convulsive seizure free days will be summed for the baseline and T+M periods and will be analyzed with a similar approach to the primary efficacy endpoint.

- *Responder Analyses: Proportion of Patients with ≥25% or ≥75% Reduction from Baseline in Convulsive Seizure Frequency*
  A step-function response curve will be generated for the mITT population. This graph will plot the % of subjects (y-axis) against percentage reduction in seizure frequency per 28 days in the T+M period (x-axis) …
  - *The proportion achieving a ≥25% reduction from baseline in convulsive seizures will be analyzed using the same method employed for the ≥50% reduction from baseline endpoint.*
  - *The proportion achieving a ≥75% reduction from baseline in convulsive seizures will be analyzed using the same method employed for the ≥50% reduction from baseline endpoint.*

Safety Analyses

- Assessment of differences in incidence, type and severity of AEs, Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, ECG, Echocardiograms, laboratory safety parameters, physical examination parameters, and Tanner staging of patients taking FEN compared with placebo.
- Cardiovascular safety will be presented in a separate safety analysis
- All safety summaries will be based on the SAF Population.

Protocol Amendments

There were 3 protocol amendments for Study 1504-C2. Important modifications to the protocol are summarized in Table 20 below.

Table 20: Summary of Major Protocol Amendments, Study 1504-C2

Amendment Number	Date	Major Changes
1	25 MAY 2016	• Addition of 24-month cardiac safety follow-up for subjects who have completed more than 13 weeks of double-blind or open-label treatment with study medication (France, The Netherlands, and Germany)
2	29 DEC 2016	• Assign the ZX008 dose of 0.5 mg/kg/day; maximum 20 mg/day for Cohort 2, and update study schedule of assessments for this dose • Clarify that cognitive function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF
3	2 FEB 2018	• Increase of number of screened/randomized patients to 115/90 based on results of Study 1 • Addition of secondary efficacy endpoints • Clarification of the multiplicity testing • Revision of AESIs after meeting with the Division

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that Study 1 was conducted in in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. The Applicant additionally stated that informed consent and assent, if possible, were obtained prior to carrying out any study procedures. The informed consent forms (ICF), protocol, and amendments for this trial were submitted to and approved by the IRB or independent ethics committee (IEC) at each participating trial site.

Financial Disclosure

In the financial disclosure summary, the Applicant identified no investigators with disclosable financial interests in Study 1504-C2.

Patient Disposition

The first patient was enrolled into Study 1504-C2 on 27 JAN 2017, and the date of the last patient's last visit was 05 JUN 2018. A total of 115 patients were screened for enrollment into Study 1504-C2. As seen in Table 21, 87 patients (75.7%) were randomized to study treatment in a 1:1 ratio to placebo (n=44) and FEN 0.5 mg/kg/day (n=43). Two patients (both from the placebo group) are not included in the mITT dataset due to inadequate baseline seizure frequency after retrospectively modified seizure data were excluded. Seventy-seven patients (88.5%) completed the study: 41 (93.2%) in the placebo group and 36 (83.7%) in the FEN group. More patients discontinued from the FEN group (7/43, 16.3%) than from the placebo group (3/44, 6.8%).

There are differences between the Applicant's and FDA's disposition analyses with respect to the reasons for early discontinuation. In the FDA analysis, the most common reason for discontinuation in both groups was AE, which occurred in 3 patients in each group (FEN0.5 mg: 7.0%, placebo: 6.8%). Other reasons for discontinuation occurred in 1 patient each: Echo Findings, Lack of Efficacy, Physician Decision, and Withdrawal by Subject.

In the disposition analysis in the CSR for Study 1504-C2, the Applicant adjudicated the reason for discontinuation of four patients as "Other". The specific reasons for early termination for three of these patients were as follows: Subj [redacted] (b) (6) (placebo) withdrew due to *"uncontrolled seizures"*, Subj [redacted] (b) (6) (placebo) because *"The subject roll over earlier into the open label study with the sponsor approval"*, and Subj [redacted] (b) (6) (FEN) because *"subject went from v7 to v12 due to worsening seizures; approved by MM and Sponsor to go into OLE early"*. Upon review of the study report and eCRFs, the underlying reason for early withdrawal from Study 1504-C2 for these three patients was increased seizures. Therefore, for the purposes of the disposition analysis, these patients' reasons for withdrawal from the study have been revised to adverse event.

Subj (b) (6) (FEN 0.5 mg/kg/day) discontinued early due to an ECHO finding when mild mitral regurgitation (MR) was identified in the ECHO performed at Visit 8. However, review of this patient's ECHO reports revealed that mild MR had been present in the initial screening ECHO but was not identified at a subsequent rescreening ECHO, which allowed the subject to be inappropriately enrolled into the study. Because it was seen in a screening ECHO, the mild MR was not considered a new finding. His follow-up ECHO 3 months after discontinuation of FEN showed trace MR.

Table 21: Disposition Events by Arm for Exposed Patients, Study 1504-C2

	Placebo (N=44) N (%)	FEN 0.5 mg/kg/day (N=43) N (%)	Total (N=87) N (%)
Completed	41 (93.2)	36 (83.7)	77 (88.5)
Terminated Early	3 (6.8)	7 (16.3)	10 (11.5)
Adverse Event*	3 (6.8)	3 (7.0)	6 (6.9)
Other (Echo Findings)	0	1 (2.3)	1 (1.1)
Lack of Efficacy	0	1 (2.3)	1 (1.1)
Physician Decision	0	1 (2.3)	1 (1.1)
Withdrawal by Subject	0	1 (2.3)	1 (1.1)

*Includes three more patients (one in the FEN group and two in the placebo group) who discontinued participation due to increased seizures.
Source: ADSL (revised, verified in JMP)

Reviewer's comment: Although the overall numbers and percent of patients who discontinued participation during the treatment period of Study 1504-C2 were small, there was an imbalance between the two groups. Specifically, the completion rate for the placebo group (93.2%) was greater than in the treatment group (83.7%), and the reasons for discontinuation differed between groups. Similar proportions of patients exited Study 1504-C2 early due to AEs (6.8% of the placebo group and 7% of the FEN 0.5 mg/kg group).

Protocol Violations/Deviations

A total of 85 (97.7%) of patients had at least one major or minor protocol deviation. Fifty-six (64.4%) of patients in Study 1504-C2 had a total of 95 major protocol violations. The most frequently occurring major protocol deviation was related to the informed consent in 20 (45.5%) patients in the placebo group and 9 (20.9%) in patients in the FEN group. All of these were due to a delay in signing an information update about preclinical data added to the Investigator Brochure.

Eleven patients had major protocol violations related to enrollment, 6 patients in the placebo group (13.6%) and 5 in the FEN group (11.6%). Reasons included compliance of diary entry by caregiver; age greater than 19 years; and failure to meet inclusion criterion requiring taking both VPA and CLB. (A subsequent protocol amendment allowed enrollment of subjects on STP plus CLB and/or VPA if either VPA or CLB were contraindicated).

Drug dosing violations occurred in 10 patients (2 placebo, 8 FEN). None of these drug-related protocol violations were prolonged.

Demographic Characteristics

Demographic characteristics of the ITT (and safety) population were generally similar between study groups (Table 22). The mean age overall was 9.1 years (placebo: 9.4 years; FEN: 8.8 years). In both groups, the majority of subjects were ≥ 6 years of age (72.7% in the placebo group and 72.1% in the FEN group). Over half of the patients were male (placebo: 61.4% and FEN: 53.5). About 25% of patients overall were from the U.S.; about 2/3 of patients were from Europe.

Table 22: Baseline Demographics (mITT Population), Study 1504-C2

Subgroup	Placebo (N = 42) n (%)	FEN 0.5 mg/kg/day (N = 43) n (%)	Total (N = 85) n (%)
Sex			
Female	16 (38.1)	20 (46.5)	36 (42.4)
Male	26 (61.9)	23 (53.5)	49 (57.6)
Age			
Mean (SD)	9.3 (5.06)	8.77 (4.56)	9.0 (4.79)
Median	9	9	9
Minimum	2, 19	2, 18	2, 19
Age Group			
<6 years	12 (28.6)	12 (27.9)	24 (28.2)
≥6 years	30 (71.4)	31 (72.1)	61 (71.8)
Race			
Asian	1 (2.4)	2 (4.7)	3 (3.5)
Black or African American	1 (2.4)	1 (2.3)	2 (2.4)
Missing	11 (26.2)	13 (30.2)	24 (28.2)
Other	1 (2.4)	3 (7.0)	4 (4.7)
White	28 (66.7)	23 (53.5)	51 (60.0)
Ethnicity			
Hispanic or Latino	7 (16.7)	3 (7.0)	10 (11.8)
Missing	15 (35.7)	15 (34.9)	30 (35.3)
Not Hispanic or Latino	20 (47.6)	25 (58.1)	45 (52.9)
Region			
Canada	3 (7.1)	4 (9.3)	7 (8.2)
Europe	29 (69.0)	28 (65.1)	57 (67.1)
United States	10 (23.8)	11 (25.6)	21 (24.7)
Height (m)			
Mean (SD)	1.30 (0.239)	1.31 (0.235)	1.31 (0.236)
Median	1.33	1.32	1.32
Baseline Weight (kg)			

Subgroup	Placebo (N = 42) n (%)	FEN 0.5 mg/kg/day (N = 43) n (%)	Total (N = 85) n (%)
Mean (SD)	35.3 (19.95)	31.3 (14.85)	33.3 (17.57)
Median	30.5	27.9	28.6
Baseline BMI (kg/m2)			
Mean (SD)	19.17 (4.923)	17.32 (2.715)	18.2 (4.047)
Median	17.51	16.58	17.13

Source: ADSL (JMP, verified)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease characteristics and concomitant drugs were generally similar between the FEN and placebo groups in Study 1504-C2 (Table 23). All patients were taking concomitant STP. The other commonly used AEDs overall in Study 1504-C2 were CLB (94.3%) and VPA (75.8%). The only AED with ≥10% difference between groups was TPM in 15.9% of patients on placebo and 32.6% in the FEN group.

More patients in the placebo group (64%) than in the FEN group (47%) had nonconvulsive seizures; the mean baseline nonconvulsive seizure frequency in the placebo group (112.36) was also greater than in the FEN group (38.74). As nonconvulsive seizures is not the primary or a key secondary efficacy outcome, this difference does not impact the efficacy determination.

Table 23: Baseline characteristics (mITT population), Study 1504-C2

	Placebo (N = 42) n (%)	FEN 0.5 mg/kg/day (N = 43) n (%)	Total (N = 85) n (%)
Baseline Convulsive Seizure Frequency			
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	
Baseline Nonconvulsive Seizure Frequency			
N (%)	27 (64.3)	20 (46.5)	
Mean (SD)	112.36 (438.215)	38.74 (67.617)	
Median	4.00	11.92	
Min, Max	0.7, 2287.3	2.2, 224.0	
Number of concomitant AEDs			
2	1 (2.3)	1 (2.3)	2 (2.3)
3	26 (59.1)	19 (44.2)	45 (51.7)
4	16 (36.4)	16 (37.2)	32 (36.8)
5	1 (2.3)	7 (16.3)	8 (9.2)
Concomitant AEDs			
Acetazolamide	0 (0.0)	2 (4.7)	2 (2.4)
Clobazam	40 (95.2)	40 (93.0)	80 (94.1)
Clonazepam	2 (4.8)	2 (4.7)	4 (4.7)

	Placebo (N = 42) n (%)	FEN 0.5 mg/kg/day (N = 43) n (%)	Total (N = 85) n (%)
Diazepam	0 (0.0)	2 (4.7)	2 (2.4)
Ergenyl Chrono	5 (11.9)	6 (14.0)	11 (12.6)
Ethosuximide	1 (2.4)	1 (2.3)	2 (2.4)
Felbamate	0 (0.0)	1 (2.3)	1 (1.2)
Gamma-aminobutyric Acid	0 (0.0)	1 (2.3)	1 (1.2)
Levetiracetam	4 (11.4)	5 (11.6)	9 (10.6)
Lorazepam	1 (2.4)	3 (7.0)	4 (4.7)
Phenobarbital	1 (2.4)	0 (0.0)	1 (1.2)
Pregabalin	1 (2.4)	1 (2.3)	2 (2.4)
Stiripentol	44 (100.0)	43 (100.0)	87 (100.0)
Topiramate	7 (16.7)	14 (32.6)	21 (24.7)
Valproate semisodium	9 (21.4)	8 (18.6)	17 (20.0)
Valproate sodium	16 (38.1)	17 (39.5)	33 (38.8)
Valproic acid	8 (19.0)	7 (16.3)	15 (17.6)
Any form of Valproate	33 (78.6)	32 (74.4)	55 (76.5)
Zonisamide	3 (7.1)	0 (0.0)	3 (3.4)
Other Treatments for Seizures			
Ketogenic diet	1 (2.4)	3 (7.0)	4 (4.7)
Vagus nerve stimulator	3 (7.1)	2 (4.7)	5 (5.9)

Source: Study 1504-C2 ADCM, ADSL (verified in JMP) and Table 29 in CSR, using the revised mITT population

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by input into the electronic diary and measurement of the residual IMP at each study visit. When compliance was measured as a percentage of assigned dose taken, most patients had ≥90% compliance in all groups (97.7% in both treatment groups).

A total of 7 patients overall missed at least one full day of study drug based on electronic diary reports. Five patients (5.7%) were reported by caregivers to have missed taking their study drug completely on a single day (placebo: 4.5%, FEN: 7%). One patient in each treatment group were reported to have missed their study drug completely on 2 days. Caregivers reported partial doses given at least once during Study 1504-C2 to 15 patients (8 placebo [18.1%] and 7 FEN [16.3%]), with most of these instances occurring one time (8 overall).

As seen in Table 24 below, the percentage of patients who used at least one dose of rescue medication during the baseline period was greater in the FEN 0.5 mg/kg/day group (65.1%) than in the placebo group (43.2%). During the treatment period, usage of rescue medications was numerically higher in patients randomized to FEN (58.1%) than in patients randomized to placebo (52.3%), but this difference was small.

Table 24: Patients with at least one use of rescue medication, Study 1504-C2

	Placebo (N=42)	FEN 0.5 mg/kg/day (N=43)
Baseline Period	19 (43.2%)	28 (65.1%)
T+M Period	23 (52.3%)	25 (58.1%)

Source: Study 1504-C2, CSR, Table 14.2.7.1b

Efficacy Results – Primary Endpoint

All patients who were randomized, received at least 1 dose of study drug, and had at least one post-baseline efficacy endpoint were included in the ITT analysis dataset, per their allocated treatment group: 43 in the (49.4%) the FEN 0.5 mg/kg/day group and 44 (50.6%) in the placebo group. The primary efficacy analyses were conducted on the mITT analysis set, which comprised a total of 85 patients; two patients from the placebo group were excluded from the mITT dataset, because the baseline convulsive seizure frequencies were missing or zero after the retrospectively modified seizure data were excluded.

As noted above, the primary efficacy endpoint was the change from baseline in the mean convulsive seizure frequency per 28 days during the treatment (titration + maintenance) period for the 0.5 mg/kg/day group compared to placebo. Compared to the placebo group, the FEN 0.5 mg group had fewer seizures on average during the treatment period (Table 25). The percentage of difference relative to placebo was -59.5% for the FEN group, which was statistically significant, in favor of FEN (p <0.001).

Reviewer's comment: Compared with the placebo group, the FEN treatment group demonstrated a statistically significant reduction in convulsive seizures from baseline to the treatment period. As noted above, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint may differ based on the underlying disease. The findings are both statistically significant (p <0.001) and clinically meaningful.

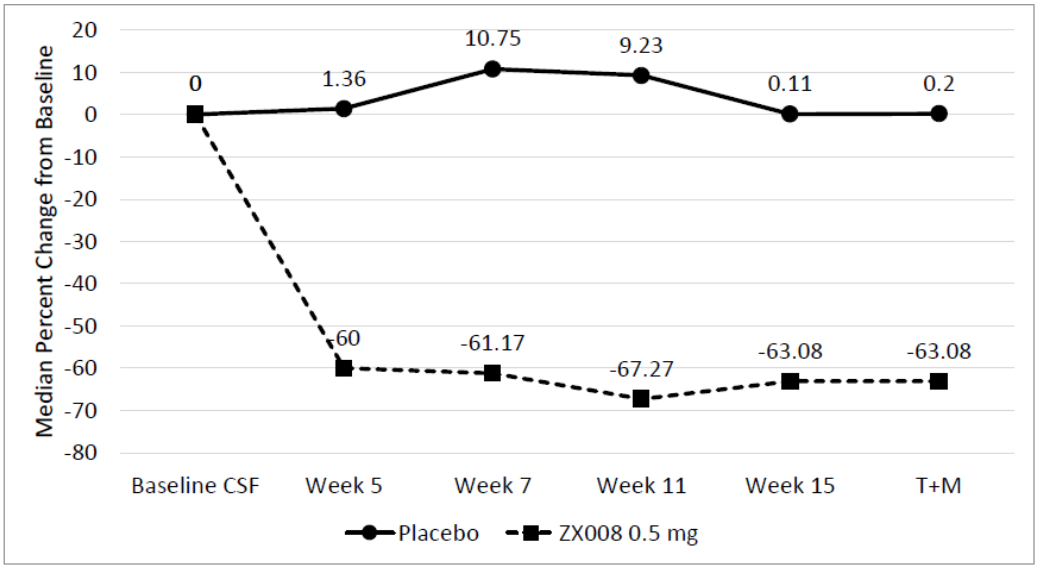
Table 25: Primary Efficacy Endpoint Results, Study 1504-C2

Convulsive Seizure Frequency per 28 days	Placebo	FEN 0.5 mg/kg/day
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 (Results on log scale) [1]		
Least Squares Mean (SE) [1]	2.77 (0.147)	1.96 (0.144)
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

Source: selected from Table 14.2.1.2b_110d (IR response from Applicant, 31 MAR 2020)
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 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 as a covariate and log convulsive seizure frequency Titration + Maintenance period as response. The p-value is obtained from this ANCOVA model.

Consistent results were seen for the maintenance period and each 4-week period of the maintenance, as seen in Figure 3.

Figure 3: Median Percent Change in Convulsive Seizure Frequency During T+M, Study 1504-C2



Source: Figure 2, Applicant's response to IR 31 MAR 2020

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, and region. The results favored the 0.5 FEN group over placebo in all subgroups and are summarized in Table 26 below.

Table 26: Subgroup Analyses of the Primary Endpoint (Demographics), Study 1504-C2

Subgroup Item	Treatment	N	Baseline Mean	Treatment Mean	Least Squares Mean (95%CI)	Estimate of A-P (95%CI)
<6 years	Placebo	12	13.33	11.81	2.26 (0.224)	
	0.5 mg/kg	12	10.57	6.74	1.45 (0.224)	-0.81 (-1.43, -0.19)
≥6 years	Placebo	30	27.18	26.55	2.99 (0.170)	
	0.5 mg/kg	31	36.61	34.68	2.17 (0.168)	-0.83 (-1.30, -0.36)
Male	Placebo	26	20.96	22.01	2.71 (0.173)	
	0.5 mg/kg	23	25.99	16.64	1.92 (0.183)	-0.80 (-1.26, -0.33)
Female	Placebo	16	26.89	22.86	2.84 (0.260)	
	0.5 mg/kg	20	33.19	38.65	2.10 (0.233)	-0.74 (-1.38, -0.11)
White	Placebo	28	25.42	23.24	2.91 (0.187)	
	0.5 mg/kg	23	38.44	43.35	2.45 (0.200)	-0.46 (-0.96, 0.04)
Non-white	Placebo	14	18.83	20.53	2.65 (0.235)	
	0.5 mg/kg	20	18.87	7.94	1.36 (0.195)	-1.29 (-1.87, -0.71)
U.S.	Placebo	10	20.92	21.30	3.59 (0.432)	
	0.5 mg/kg	11	55.63	77.19	3.05 (0.361)	-0.54 (-1.48, 0.40)
Non-U.S.	Placebo	32	23.94	22.66	2.62 (0.146)	
	0.5 mg/kg	32	20.31	9.59	1.64 (0.146)	-0.98 (-1.37, -0.59)
Clobazam (yes)	Placebo	40	22.92	22.00	2.79 (0.15)	
	0.5 mg/kg	40	30.83	28.51	1.94 (0.15)	-0.85 (-1.25, -0.45)
Clobazam (no)	Placebo	2	29.14	29.08	2.79 (0.15)	
	0.5 mg/kg	3	9.49	5.11	1.84 (1.11)	-0.84 (-28.09, 26.41)
Valproate (yes)	Placebo	33	23.95	21.93	2.73 (0.17)	
	0.5 mg/kg	32	27.81	17.12	1.94 (0.16)	-0.79 (-1.23, -0.34)
Valproate (no)	Placebo	9	20.55	23.82	2.91 (0.30)	
	0.5 mg/kg	11	33.79	55.27	1.97 (0.29)	-0.94 (-1.72, -0.17)

Source: From Table 14.2.1.2b_110d, Response to IR 31 MAR 2020, verified by FDA statistical reviewer

Data Quality and Integrity

See Section 4.1 for a discussion of the significant data integrity issues seen in Study 1504-C2.

Other issues related to the efficacy datasets identified by Dr. Zhang included incorrect application of end-of-treatment-period dates and seizures that were counted as both baseline seizures and seizures on day 1 of treatment. The efficacy dataset included seizures outside of the prespecified window for the treatment period (last day of treatment in the SAP was day 110). For example, one patient's data was derived from diary data from study day 1 to study day 131. Some seizures were flagged as baseline seizures and double-counted as convulsive seizures on study day 1 in 18 patients. These issues were conveyed to the Applicant in IR's in December 2019 and revised datasets were provided in January 2020.

Efficacy Results – Secondary and other relevant endpoints

The prespecified key secondary endpoints for Study 1504-C2 were the 50% responder rate and median longest interval between convulsive seizures and are summarized in Table 27 below.

- Proportion of patients with ≥50% reduction in convulsive seizure frequency
  During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the FEN group (53.5%), compared with the placebo group (4.8%). This difference was statistically significantly in favor of the FEN group ($p < 0.001$).

- Median longest interval between convulsive seizures
  The longest interval between convulsive seizures is the maximum of the number of days between consecutive convulsive seizures. If there was a single day with missing diary information between two days without seizures ("no-seizure days"), this missing day was treated as also as "no-seizure" day, in the Applicant's initial analysis. When all days with missing data were considered to be days with seizures (conservative approach), the median longest interval between convulsive seizures were 12.0 days and 17.0 days for the placebo and FEN 0.5 mg/kg/day groups, respectively. The FEN and placebo comparison remained statistically significant (p=0.010).

Table 27: Key Secondary Endpoints Results, Study 1504-C2

	Statistic	mITT Parametric Analysis	
		Placebo	FEN 0.5 mg/kg/day
Proportion of ≥50% Responders	N	42	43
	Patients Experienced, n(%)	2 (4.8)	23 (53.5)
	OR (95%CI)		25.453 (5.288, 122.500)
	p-value		<0.001

	Statistic	mITT Parametric Analysis	
		Placebo	FEN 0.5 mg/kg/day
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 (Conservative approach)	N	42	43
	Median (days)	12.0	17.0
	p-value		0.010

Source: Table D, IR response dated 31 MAR 2020

Reviewer's comment: The results of the key secondary analyses are statistically significant and generally supportive of the primary efficacy endpoint. The proportion of patients with a ≥50% reduction in convulsive seizure frequency analysis (50% responder analysis) is not independent of the primary efficacy outcome and, while helpful in defining a subset of patients who might be considered responders, does not provide information separate from the primary efficacy endpoint.

The longest interval between convulsive seizures provides information on duration of time between the most disabling seizures experienced by patients with DS. As with the 50% responder analysis, it is not completely independent of the primary efficacy outcome. It is not an outcome measure frequently used in AED treatment trials, but it is clinically meaningful and is supportive of the primary efficacy endpoint.

Other Secondary Endpoints of Clinical Interest

- Nonconvulsive Seizures

  Nonconvulsive seizures were reported during baseline in 46.5% of 0.5 mg/kg/day patients and 64.3% of placebo patients in the mITT analysis set. As seen in Table 28 below, a greater median reduction from baseline in nonconvulsive seizure frequency during the treatment period was seen in the placebo group, compared with the 0.5 mg/kg/day group.

Table 28: Change from Baseline in Nonconvulsive Seizures, Study 1504-C2

	Placebo (N=43)	FEN 0.5 mg/kg/day (N=42)
Baseline Summary Statistics		
N	27	20
Mean (SD)	112.36 (438.215)	38.74 (67.617)
Median	4.00	11.92
Min, Max	0.7, 2287.3	2.2, 224.0
T+M Period Summary Statistics		
N	27	20
Mean (SD)	84.28 (338.536)	71.66 (162.108)
Median	2.20	6.91

	Placebo (N=43)	FEN 0.5 mg/kg/day (N=42)
Min, Max	0.0, 1757.3	0.0, 560.7
Change from Baseline		
N	27	20
Mean (SD)	-27.08 (102.983)	32.92 (97.733)
Median	-2.67	-2.38
Min, Max	-530.1, 43.2	-29.5, 336.7
Percent Change from Baseline		
N	27	20
Mean (SD)	-28.07 (120.415)	-8.21 (100.183)
Median	-62.49	-14.08
Min, Max	-100.0, 480.1	-100.0, 243.4

Source: Table 14, Response to IR dated 31 MAR 2020

Reviewer's comment: Although not pre-specified in the SAP as a hierarchical secondary endpoint for the purposes of statistical analysis, change in nonconvulsive seizures is an important endpoint from the clinical perspective. A general concern with epilepsy disorders in which there are frequent multiple seizure types, is that a treatment may improve one type of seizures and worsen another. Nonconvulsive seizures, while not as disabling as convulsive seizures, still cause significant morbidity for patients with DS. The analysis of change in mean nonconvulsive seizure frequency favors the placebo group over the FEN 0.5 mg/kg group, although both groups showed a reduction from baseline.

- Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom

  A higher proportion of patients in the 0.5 mg/kg FEN group had a ≥25% reduction in convulsive seizure frequency from baseline during the treatment period compared with patients in the placebo group (67.4% vs. 23.8%, respectively), while39.5% of patients in the FEN 0.5 mg/kg group achieved a ≥75% reduction in convulsive seizure frequency during the treatment period compared with 4.8% in the placebo group. One patient in the 0.5 mg group and 0 patients in the placebo group had no convulsive seizures during the treatment period. See Table 29 below for specifics.

Table 29: Summary and Analysis of Convulsive Seizure Treatment Responders, Study 1504-C2

	Placebo (N=42)	0.5 mg/kg (N=43)
≥25% Reduction		
Yes	10 (23.8%)	29 (67.4%)
Odds Ratio (95% CI) [Active/Placebo]		6.944 (2.620, 18.409)
≥50% Reduction		
Yes	2 (4.8%)	23 (53.5%)

	Placebo (N=42)	0.5 mg/kg (N=43)
Odds Ratio (95% CI) [Active/Placebo]		25.453 (5.288, 122.500)
p-value*		<0.001
≥75% Reduction		
Yes	2 (4.8%)	17 (39.5%)
Odds Ratio (95% CI) [Active/Placebo]		13.761 (2.888, 65.571)
100% Reduction		
Yes	0 (0.0%)	1 (2.3%)

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.
**Two separate logistic regression models that include a categorical response variable (achieved xx percentage point reduction, yes or no) as a function of treatment group (Active or placebo), age group (< 6 years1 ~ 6 years) and baseline convulsive seizure frequency were used.*
Source: Modified from Table 6, Response to IR dated 31 MAR 2020

Clinical reviewer's comment: Overall, the responder analysis favored FEN over placebo. The difference between the FEN and placebo groups is notable for the ≥25% and ≥75% responders and is statistically significant for the ≥50% responders. Because of the small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of FEN over placebo. Of note is the difference between FEN and placebo with respect to 0 convulsive seizures (1 patient in the FEN group and 0 in the placebo group. No seizures during a prolonged treatment period is a clinically meaningful outcome, especially in this particularly refractory epilepsy syndrome. The difference between FEN and placebo is small but notable.

- Patient/Caregiver Global Impression of Improvement (CGI-I)
  For the analysis of CGI-I score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. The number (%) of patients who were rated as showing improvement (had a score of "minimally improved", "much improved", or "very much improved") for the FEN 0.5 mg and placebo groups at the EOS visit were 31 (72.1) and 14 (31.8). The treatment differences were in favor of the FEN 0.5 mg/kg group (OR=5.3) as seen in Table 30.

Table 30: Patient/Caregiver Global Impression of Improvement (CGI-I), Study 1504-C2

Summary Description	Placebo (N=42)	FEN 0.5 mg/kg (N=43)
Visit 12 Summary Statistics		
n	40	42
Mean (SE)	3.5 (0.17)	2.7 (0.20)
Median	4.0	3.0
Min, Max	1, 6	1, 6
Number and percentage of subjects with CGI scales at Visit 12		
1= Very much improved	3 (6.8)	8 (18.6)
2= Much improved	4 (9.1)	11 (25.6)
3= Minimally improved	7 (15.9)	12 (27.9)
4= No change	23 (52.3)	9 (20.9)
5= Minimally worse	2 (4.5)	0 (0.0)
6= Much worse	1 (2.3)	2 (4.7)
7= Very much worse	0 (0.0)	0 (0.0)
Improvement		
Improved (1,2,3) n(%)	14 (31.8)	31 (72.1)
Odds Ratio vs. placebo		5.2 (2.03, 13.52)
"Clinically Meaningful" Improvement		
Much improved or very much improved (1, 2) n(%)	7 (15.9)	19 (44.2)
Odds Ratio vs. placebo		3.9 (1.40, 10.64)

Source: Table 33, Study 1504-C2 CSR

Dose/Dose Response

See Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance period. Consistent results were seen for both doses of FEN for each of these time periods in Study 1504-C2. See also Section 7.1.5.

Additional Analyses Conducted on the Individual Trial

Overall, 74/85 (87.1%) of the patients in the mITT population of Study 1504-C2 were found to have a mutation of the SCN1A gene, 37 (88.1%) and 37 (86.0%) in the placebo and 0.5 mg/kg groups, respectively.

Table 31 below shows a greater reduction in mean convulsive seizure frequency per 28 days from baseline in the FEN group compared to placebo in patients with or without SCN1A gene mutations.

Table 31: Subgroup Analysis of the Primary Endpoint by SCN1A status, Study 1504-C2

	Placebo		FEN 0.5 mg/kg/day	
	SCN1A+	SCN1A-	SCN1A+	SCN1A-
Baseline Summary Statistics				
N	37	5	37	6
Mean (SD)	25.85 (29.76)	3.77 (2.52)	31.16 (40.32)	18.11 (15.09)
Median	16.80	5.33	15.02	15.02
Min, Max	2.67, 162.67	0.74, 6.00	2.00, 213.33	4.42, 39.20
T+M Period Summary Statistics				
N	37	5	37	6
Mean (SD)	24.64 (29.53)	5.32 (2.26)	29.12 (79.98)	13.07 (17.22)
Median	14.82	5.50	5.03	3.88
Min, Max	2.38, 170.13	2.38, 8.40	0.00, 469.00	0.25, 38.18
T+M Period: Parametric Model Summary (results on a log scale)				
Least Squares Mean (SE)	2.82 (0.16)	2.49 (0.50)	2.04 (0.16)	1.26 (0.45)
Estimate of A-P (95% CI)			-0.78 (-1.19, -0.36)	-1.23 (-2.98, 0.52)

SCN1A+ = patients with any reported mutation in the SCN1A gene during the trial.
SCN1A- = patients without any reported mutation in the SCN1A gene
Source: FDA statistician

Reviewer's Comments: Both FEN groups demonstrated greater reduction in mean convulsive seizure frequency from baseline compared to placebo regardless of SCN1A status, suggesting that presence or absence of mutations of the SCN1A gene are not a factor in response to FEN. As this subgroup analysis was not prespecified in the SAP, p-values are not reported.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This application contains data from two pivotal trials to support the indication of treatment of seizures in Dravet syndrome in patients 2 years of age and older.

7.1.1. Primary Endpoints

Reduction in convulsive seizures was the efficacy outcome measure used in Studies 1 and 1504-C2, and the primary efficacy endpoint was defined as change in the mean convulsive seizure frequency per 28 days between baseline and treatment (titration+maintenance) periods. The

primary efficacy endpoint was not assessed at one specific time but was rather a measure of change in seizure frequency over the entire treatment period, which included the titration period (2 weeks in Study 1 and 3 weeks in Study 1504-C2) and the 12-week maintenance period. Convulsive seizures were defined in the protocol as generalized tonic-clonic, tonic, clonic, tonic-atonic, hemiclonic, and focal seizures with an observable motor component. As noted elsewhere in this review, change from baseline in seizure frequency (average per 28 days) during the treatment period is the most frequently used primary efficacy endpoint for AED treatment trials.

Both trials used the same diagnostic criteria for DS and the almost identical eligibility criteria. The major difference between the two studies was that Study 1 excluded patients taking concomitant stiripentol, while all patients in Study 1504-C2 were required to be taking concomitant stiripentol. The study populations in Studies 1 and 1504-C2 were very similar based on baseline demographics and disease-related characteristics (Tables 8, 9, 22, and 23).

The effectiveness of FEN for the treatment of convulsive seizures associated with DS was established in patients ages 2 years and older, as seen in Table 32 below. Study 1 (N=117) compared two doses of FEN (0.2 mg/kg/day and 0.8 mg/kg/day) with placebo. Study 1504-C2 compared FEN (0.5 mg/kg/day) with placebo. A greater proportion of the FEN 0.8 mg/kg group (15%) in Study 1 and the FEN 0.5 mg/kg group (16.3%) in Study 1504-C2 withdrew during the treatment period than the placebo groups in Studies 1 and 1504-C2 (10% and 6.8%, respectively) or the 0.2 mg/kg/day group (0%).

In Study 1, there were statistically significant differences between each FEN group and the placebo group in the change from baseline in mean convulsive seizure frequency during the treatment period, favoring FEN (p <0.001 and p=0.043, respectively). The percentages of difference relative to placebo were -31.7% and -70.0% for the FEN 0.2 mg/kg and FEN 0.8 mg/kg groups, respectively. The analysis results were generally consistent across subgroups. In Study 1504-C2, there was statistically significant difference between the groups in the change from baseline in mean convulsive seizure frequency during the treatment period, in favor of FEN treatment (p=0.0135), and the percentage of difference relative to placebo was -59.5% for the FEN group. The analysis results were generally consistent across subgroups.

Table 32: Summary Comparison of Primary Efficacy Analyses, Studies 1 and 1504-C2

	Study 1			Study 1504-C2	
	Placebo (N=39)	FEN 0.2 mg/kg/day (N=38)	FEN 0.8 mg/kg/day (N=40)	Placebo (N=43)	FEN 0.5 mg/kg/day (N=42)
Baseline Period Mean	45.47 (40.691)	45.29 (101.054)	32.93 (32.332)	23.22 (28.818)	29.34 (37.963)
Treatment Period Mean	38.25 (36.959)	26.99 (38.729)	18.60 (32.497)	22.34 (28.399)	26.88 (74.497)
Least Squares Mean (on log scale)	3.04 (0.128)	2.68 (0.131)	1.94 (0.126)	2.77 (0.147)	1.96 (0.144)

	Study 1			Study 1504-C2	
	Placebo (N=39)	FEN 0.2 mg/kg/day (N=38)	FEN 0.8 mg/kg/day (N=40)	Placebo (N=43)	FEN 0.5 mg/kg/day (N=42)
Estimate of A-P (95%CI)		-0.36 (-0.70, -0.02)	-1.10 (-1.44, -0.76)	−17.2 (−30.3, −4.1)	-0.82 (-1.19, -0.44)
P-value by Wilcoxon rank-sum test		0.043	<0.001		<0.001

7.1.2. Secondary and Other Endpoints

Studies 1 and 1504-C2 prespecified a hierarchical examination of the same two key secondary endpoints, although these endpoints were examined for both FEN dose groups in Study 1504-C2. All of the prespecified key secondary analyses favored FEN over placebo with statistically significant results (Table 33) and are supportive of the efficacy of FEN in the treatment of convulsive seizures in patient with DS.

Key Secondary Endpoints

- Proportion of patients with ≥50% reduction in seizures
  During the treatment period in Study 1, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the 0.8 mg/kg and 0.2 mg/kg FEN groups, compared with the placebo group. The odds ratios (ORs) were statistically significant for both the 0.8 mg/kg/day group (OR =29.2; p <0.001) and the 0.2 mg/kg/day group (OR =6.9; p=0.007). In Study 1504-C2, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was also greater in the FEN 0.5 mg group, compared with the placebo group. The odds ratios (OR) was 25.4 and achieved statistical significance (p <0.001).

- Median longest interval between convulsive seizures
  The longest interval between convulsive seizures measured the maximum of the number of days between consecutive convulsive seizures. In Study 1, the median longest interval between convulsive seizures were 20.5 days and 13.0 days for the FEN 0.8 mg/kg and 0.2 mg/kg groups, respectively, compared to placebo (8.0 days). These results were statistically significant (p-value = 0.010). In Study 1504-C2, the median longest interval between convulsive seizures were 12.0 days and 17.0 days for the placebo group and FEN 0.5 mg/kg/day group, respectively, and statistically significant (p<0.001 and p=0.043).

Table 33: Summary Comparison of Key Secondary Efficacy Analyses, Studies 1 and 1504-C2

Variable	Study 1			Study 1504-C2	
	Placebo (N=39)	FEN 0.2 mg/kg/day (N=38)	FEN 0.8 mg/kg/day (N=40)	Placebo (N=43)	FEN 0.5 mg/kg/day (N=42)
≥ 50% Reduction in Convulsive seizure Frequency					
n (%)	3 (7.7)	13 (34.2)	28 (70)	2 (4.8)	23 (53.5)
Odds Ratio (95% CI)		6.9 (1.69, 28.12)	29.2 (7.10, 120.46)		25.5 (5.29, 122.50)
P-value by CMH test		0.007	<0.001		<0.001
Median Longest Interval Between Convulsive Seizures (Conservative approach)					
Median (days)	8.0	13.0	20.5	12.0	17.0
p-value		0.043	<0.001		

Source: Tables B and D, IR response 31 MAR 2020

Other Secondary Endpoints of Clinical Relevance

- **Change in Percentage of Nonconvulsive Seizures**
  Although not pre-specified in the SAP for either Study 1 or 1504-C2 as a hierarchical secondary endpoint for the purposes of statistical analysis, change in nonconvulsive seizures is an important clinical endpoint. In epilepsy disorders in which there are frequent multiple seizure types, treatment may improve one type of seizures and worsen another. Nonconvulsive seizures, while not as disabling as convulsive seizures, still cause significant morbidity for patients with DS. Nonconvulsive seizures are typically not included in the primary efficacy endpoint of treatment trials for disorders such as Dravet syndrome due to lower disability and lack of reliability in counting such seizures but are analyzed as a "safety" measure to be sure there is no increase in nonconvulsive seizures in the setting of decreased convulsive seizure frequency.

  As seen in Table 34 below, a reduction in the nonconvulsive seizure frequency from baseline during the treatment period was seen in all three FEN groups and both placebo groups. The reduction in nonconvulsive seizure frequency was notably greater in the 0.8 mg/kg group compared to placebo, no different between the 0.2 mg/kg group and placebo, and lower in the 0.5 mg/kg FEN group compared to placebo. In general, these findings do not demonstrate an increase in nonconvulsive seizure frequency and are supportive of the proposed indication.

Table 34: Comparison of Analyses of Nonconvulsive Seizures, Studies 1 and 1504-C2

Nonconvulsive seizures	Study 1			Study 1504-C2	
	Placebo (N=39)	FEN 0.2 mg (N=38)	FEN 0.8 mg (N=40)	Placebo (N=43)	FEN 0.5 mg (N=42)
n (%)	27 (69.2)	26 (68.4)	27 (67.5)	27 (62.7)	20 (47.6)
Baseline Period					
Mean	148.13	180.03	292.48	84.28	71.66

Nonconvulsive seizures	Study 1			Study 1504-C2	
	Placebo (N=39)	FEN 0.2 mg (N=38)	FEN 0.8 mg (N=40)	Placebo (N=43)	FEN 0.5 mg (N=42)
Median	18.12	22.5	32.00	2.20	6.91
Treatment Period					
Mean	110.94	90.80	112.42	84.28	71.66
Median	21.91	4.39	12.41	2.20	6.91
Change from baseline					
Mean	-37.19	-89.23	-180.06	-27.08	32.92
Median	-3.41	-3.38	-15.76	-2.67	-2.38
Percent change from baseline					
Mean	-14.32	-24.60	-63.88	-28.07	-8.21
Median	-53.57	-56.80	-76.91	-62.49	-14.08

- **Continuous Response Analysis of Convulsive Seizures**
  The Applicant included a continuous response analysis for convulsive seizures in both Studies 1 and 1504-C2 in Section 14 of the prescribing information (PI). This type of analysis, while deemed dependent on and not assessing a different domain from the primary efficacy endpoint, is frequently included in the clinical trials summaries of the PI of AEDs. The continuous response analyses are summarized in Section 6.1.2 (Table 15) and Section 6.2.2 (Table 29) for Studies 1 and 1504-C2, respectively. The results of these analyses in both trials overall favored FEN (all doses) over placebo.

- **Patient/Caregiver Global Impression of Improvement (CGI-I)**
  For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. In both studies (Table 35), the treatment differences were in favor of FEN over placebo with OR 1.8, OR=2.6, and OR=5.2 for the 0.8 mg/kg, 0.2 mg/kg, and 0.5 mg/kg groups, respectively.

Table 35: Summary Comparison of Patient/Caregiver Global Impression of Improvement (CGI-I), Studies 1 and 1504-C2

	Placebo (N=40)	FEN 0.2 mg/kg (N=39)	FEN 0.8 mg/kg (N=40)	Placebo (N=44)	FEN 0.5 mg/kg (N=43)
Summary statistics					
n	36	39	37	40	42
Mean	3.9	3.1	2.6	3.5	2.7
Median	4.0	3.0	2.0	4.0	3.0
Improvement					
Improved (1,2,3)	12 (30.0%)	22 (56.4%)	26 (65.0%)	14 (31.8%)	31 (72.1%)
OR vs. placebo		2.6	4.6		5.3

7.1.3. Subpopulations

The Applicant performed analyses of the primary efficacy endpoint on all relevant subgroups (age groups, sex, race, and region) for Studies 1 and 1504-C2 separately. Almost of the subgroup analyses favored FEN (all three doses) over placebo (as seen in Table 12 and Table 26). There was no notable difference between subgroups/treatment arms for all analyses except for that of <6 years in patients taking 0.2 mg/kg/day, in which the patients had an increase in mean convulsive seizure frequency from baseline. The sample sizes in these subgroup analyses were at times small, making it difficult to draw definitive clinical conclusions.

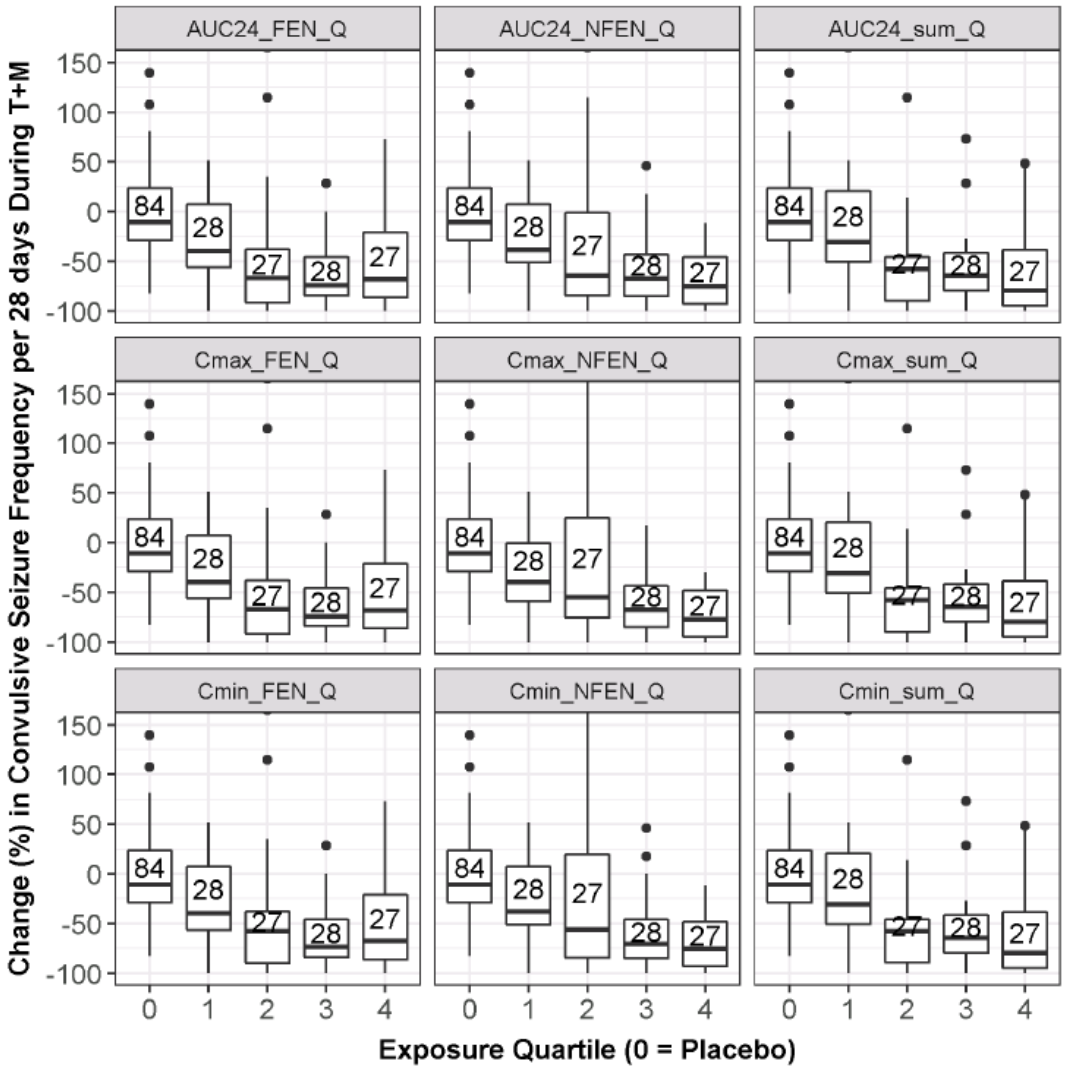
7.1.4. Dose and Dose-Response

Direct comparison of dose-response between trials was complicated by the drug-drug interaction between fenfluramine and stiripentol and the differing PK results in the dedicated STP-FEN DDI study and the PPK modeling based on data from the pivotal trials. A second issue that impacts dose-response analyses is the maximum FEN dose of 30 mg/day, regardless of dose group, in Study 1 and 20 mg/day in Study 1504-C2. The maximum dose in Study 1 would be reached in patients with a body of weight of 37.5 kg in the 0.8 mg/kg/day group and 150 kg in the 0.2 mg/kg/day group, while the maximum daily dose was reached in patients with a body weight of ≥40 kg who take 0.5 mg/kg/day. Additionally, the Applicant did not collect actual dose information in the CRFs; therefore, correlation with dose based on mgs is not possible and may impact the dose-response analyses.

The Applicant performed analyses evaluating potential relationships between PK exposure and efficacy. In the ISE, the Applicant states that there was *"a relationship between exposure and such that the median seizure frequency decreases (ie, an improvement) with increasing exposure quartile from placebo subjects through active subjects in the 2 lowest exposure quartiles. Subjects in the 2 highest exposure quartiles had similarly low seizure frequency."* This apparent relationship between efficacy and PK exposure (although perhaps not dose) is summarized in Figure 4 below.

Lastly, a significant number of patients who received the 0.2 mg/kg/day dose in Study 1 had considerable reduction in convulsive seizure frequency compared to baseline, supporting the proposal for approval of the lower dose. Given that efficacy was demonstrated with the 0.2 mg/kg/day dose (without concomitant STP), that there is no expectation that the lower dose would not also be effective in patients taking concomitant STP, that there were some dose-related adverse effects, and that dose may play a role in fenfluramine-associated VHD and PAH, the initial maintenance dose for patients should be 0.2 mg/kg/day with the option to increase, based on tolerability and need for improved seizure control to 0.8 mg/kg/day in patients not taking concomitant STP and 0.5 mg/kg/day in patients on concomitant STP. The dosing section of the label should be revised to be consistent with this proposal.

Figure 4: Box-and-Whisker Plots Showing the Distributions of Percent Change in Convulsive Seizure Frequency per 28 Days, Stratified by Exposure Quartile



Data for one patient who received placebo and had a percent change of +435% and two patients receiving 0.2 mg/kg/day who had percent changes of 198% and 165% are excluded from the above plot for visualization purposes
Source: Figure 19, ISE

The titration schedule in the PI (as of June 1, 2020) is as follows:

- *The initial starting and maintenance dose is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. Table 1 [Table 36 below] provides the recommended titration schedule, if needed.*
- *Patients not on concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximal daily dose of 26 mg/day).*

- *Patients taking concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximal daily dose of 17 mg/day) [see Drug Interactions (7.1)].*

Table 36: Recommended Titration Schedule

	Without concomitant stiripentol*		***With concomitant stiripentol***	
	Weight-based Dose	***Maximum Total Daily Dose***	***Weight-based Dose***	***Maximum Total Daily Dose***
Initial Dose	*0.1 mg/kg twice daily*	*26 mg/day*	*0.1 mg/kg twice daily*	*17 mg/day*
Day 7	*0.2 mg/kg twice daily*	*26 mg/day*	*0.15 mg/kg twice daily*	*17 mg/day*
Day 14	*0.35 mg/kg twice daily*	*26 mg/day*	*0.2 mg/kg twice daily*	*17 mg/day*

** For patients not on concomitant stiripentol in whom a requiring more rapid titration is warranted, the dose may be increased every 4 days*

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In chronic seizure disorders, such as DS, persistence of treatment effect is of interest. In Study 1, the maintenance period was defined as Day 16 to Day 99±4 days (or the day of last dose up to and including the end of treatment visit, if earlier). Maintenance period began on study day 22 and ended on study day 106±4 days in Study 1504-C2. Sensitivity analyses of the primary endpoint favored FEN at 0.8, 0.5, and 0.2 mg/kg/day over placebo in reducing convulsive seizure frequency during the maintenance period and each 4-week block. There are no controlled efficacy data in reduction of seizures in patients with DS on FEN beyond 15 weeks.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are a few issues that may arise in the postmarketing setting when the drug becomes more widely available that were not captured in the development program. The controlled clinical trials only included patients up to age 18, and the oldest patient enrolled in the OLE study was 19 years of age. Therefore, there are no data available to inform on the efficacy of the product in patients over the age of 18. The Fintepla development program also includes a study in patients with Lennox-Gastaut syndrome (LGS) which includes some adult patients. Although the DS and LGS are not the same disorder, that trial will provide some efficacy (and safety) data in adult patients with LGS which, like DS, is a severe epileptic encephalopathy.

7.2.2. Other Relevant Benefits

None.

7.3. Integrated Assessment of Effectiveness

The Applicant provided results from two randomized, double-blind, placebo-controlled pivotal

trials to support the fenfluramine in the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. Both of these studies used a primary efficacy outcome measure (reduction in frequency of convulsive seizures) and primary efficacy endpoint (percentage change from baseline in convulsive seizure frequency [average per 28 days] during the treatment period) that are considered to be a standard measure of efficacy in antiepileptic drug trials.

Study 1 provides robust statistical and clinical evidence for the efficacy of fenfluramine in the treatment of convulsive seizures. Both doses of fenfluramine (0.8 and 0.2 mg/kg/day) showed statistical superiority over placebo in the reduction of convulsive seizure frequency over the treatment period, and the results were clinically meaningful (-31.7% and -70.0% in the 0.8 mg/kg and 0.2 mg/kg groups, respectively, compared to placebo) and statistically significant ($p<0.001$ and $p=0.043$, respectively). Additionally, similar results were seen for each 4-week period during the maintenance period, suggesting no effect convulsive-off during the trial. Lastly, FEN was statistically superior over placebo in the key secondary endpoints, providing more support for the efficacy of FEN in treating seizures in patients with DS.

Study 1504-C2 also provided statistical and clinical evidence of FEN's efficacy in conjunction with stiripentol in treating convulsive seizures in patients with DS. FEN at 0.5 mg/kg/day showed statistical superiority over placebo ($p<0.001$) with a clinically meaningful reduction in convulsive seizure frequency (percentage of difference compared to placebo of −59.5%). FEN showed statistical superiority over placebo for the sensitivity analyses of the primary efficacy endpoint in each 4-week period of the maintenance period and for all three key secondary endpoints, providing support for the primary efficacy endpoint results.

Overall, there are statistically and clinically positive data from two well-designed and conducted, pivotal trials supporting the efficacy of FEN in the treatment of convulsive seizures associated with DS.

8. Review of Safety

8.1. Safety Review Approach

The Applicant conducted a development program for the indication of treatment of seizures associated with Dravet syndrome (DS). The individual studies are described in Section 6. The primary safety data were generated from the controlled safety database, which includes the data from Studies 1 and 1504-C2.

Other Controlled Data:

- Study 1504-C1: The PK and safety of a single dose of FEN when added to a regimen that include stiripentol was evaluated in Study 1504-C1. Because the patients enrolled in this study only received a single dose of FEN, and not all of the doses administered are

consistent with the dosing in the pivotal studies (and the proposed labeling), pooling with the placebo-controlled multiple-week pivotal trials was problematic. These patients were included in the Uncontrolled Safety Population.

Uncontrolled Safety Data:

- Patients who completed Studies 1, 1504-C1, and 1504-C2 had the option of continuing into an open-label extension study (Study 1503), which remains ongoing. Patients were transitioned via a blinded 2-week period to 0.2 mg/kg/day. Patients who had been randomized to FEN 0.5 or 0.8 mg/kg/day in the controlled trials had their doses decreased to 0.4 mg/kg/day for 4 days and then decreased to 0.2 mg/kg/day in a blinded manner. Patients in the 0.2 mg/kg/day group remained on their dose. Patients who had been on placebo started 0.2 mg/kg/day on the first day of the transition period.
- (b) (4)

120-Day Safety Update:
A 120-day safety update was submitted on January 23, 2020 and included an additional 98 patients enrolled into Study 1503 (cutoff date of 14 OCT 2019). My analyses of adverse events in the uncontrolled safety population include these data.

Pooling Data across Studies:
Because the study designs, patient populations, and fenfluramine doses were comparable in Studies 1 and 1504-C2, the Applicant proposed to pool safety analyses from both studies. The Division agreed with this approach. The Applicant performed their primary safety analyses on the "Core Study", which included the titration, maintenance, and taper/transition periods. Inclusion of the transition period in the blinded, controlled safety analyses is problematic, because patients in the placebo group who opted to enroll in the OLE study were exposed to FEN starting on day 1 of the transition period. Therefore, some patients in the placebo group were exposed to drug for 2 weeks of the primary safety analysis period. Because of the confounding factor of patients in the placebo groups having received FEN during the transition period of the blinded studies, my primary safety analyses were performed on the double-blind safety population during the titration and maintenance periods only. Although patients and investigators remained blinded to treatment allocation during the transition/taper period, patients in the FEN groups during the transition period are included in the uncontrolled safety population. The uncontrolled safety population also includes patients enrolled in Study 1504-C1, as all patients in that study received fenfluramine. Lastly, the uncontrolled safety population also includes patients enrolled in Study 1503 after the original data cutoff (13 MAR 2018) but prior to the cutoff date for the 120-Day Safety Update (14 OCT 2019).

The analyses in this section are based primarily on the pooled controlled safety dataset during

titration and maintenance periods only. Other analyses were performed on the uncontrolled safety dataset, which included AE data from the following groups:

- transition periods for placebo patients from Studies 1 and 1504-C2 who transitioned into the OLE study,
- transition/taper period for all FEN patients from Studies 1 and 1504-C2,
- patients enrolled in Study 1504-C1, and
- Study 1503

Analyses of Adverse Event Data:
The adae.xpt datafile was examined for accuracy of translation from verbatim to preferred term through manual review of all unique pairs of verbatim and preferred terms. Some AEs were coded under slightly different terms, although the underlying events were very similar and/or related. Therefore, several AE terms were recoded to avoid underestimating prevalence of a specific adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. The following table shows the original AE code on the left, and revised codes on the right. Terms that only resulted in the addition of one or two cases after recoding are not included in the table.

Where *additions* were made, the original record from the adverse event data file was duplicated (e.g., time of onset, intensity, severity, relatedness), and the new preferred term(s) was used. For example, the Applicant translated the verbatim term "FALL FROM SEIZURE" to the preferred term "Fall," but the seizure itself had not generated a preferred term. In such cases, the record for the fall was duplicated, and the newly inserted preferred term ("Seizure") was added on a new line below the original AE.

Grouping of related preferred terms: Applicants typically tabulate preferred terms individually, markedly reducing the apparent magnitude of safety signals. I assessed ~200 groupings of related preferred terms in my safety analyses. For example, the preferred terms "Atonic seizures", "Change in seizure presentation", "Clonic convulsion", "Febrile convulsion", "Generalised tonic-clonic seizure", "Myoclonic epilepsy", "Partial seizures", "Petit mal epilepsy", "Seizure cluster", and "Tonic convulsion" were included in the "Seizure" grouping. "Somnolence," "Sedation," and "Lethargy" were combined in a grouping, as were "Fatigue", "Asthenia", and "Malaise". See Table 41 below for specific changes and revised groupings.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

All of the safety data in the primary safety analyses were generated in Studies 1 and 1504-C2. The data from these studies provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs. The primary NDA safety database includes a total of 206 patients who were exposed to at least one dose of fenfluramine. The uncontrolled safety dataset is comprised of data from Study 1504-C1 and

Study 1503, as well as the taper/transition periods of patients randomized to fenfluramine in Studies 1 and 1504-C2. Study 1503 is an ongoing open-label, long-term safety study of fenfluramine in patients with DS, recruited from Studies 1, 2, 1504-C1, and 1504-C2.

As seen in Table 37 below, 232 patients were enrolled and randomized into Studies 1, 2, 1504-C1, and 1504-C2 and received at least one dose of fenfluramine (LTS population) and were included in the ISS safety population. A total of 206 patients were randomized in Studies 1 and 1504-C2 and received at least one dose of either FEN (n=122) or placebo (n=84) during the double-blind period (ISS-DB population). Eighteen patients were randomized into Study 1504-C1, all of whom received a single dose of FEN (ISS-PK population). The ISS-ALL population (n=224) includes all patients randomized into Studies 1, 1504-C2, and 1504-C1, regardless of treatment allocation. A total of 341 unique DS patients were exposed to FEN as of the cutoff date for the 120-day safety update.

Study 1503 was ongoing at the time of submission of this NDA. (b) (4) Because dosing in Study 1503 was flexible, duration of exposure by dose was assessed in dose groups and is summarized in Table 39.

Table 37: Number of Patients in Analysis Populations

	Core Study				N	Integrated Summary Populations		
	Study 1	Study 1504-C2	Study 1504-C1	(b) (4)		ISE	ISS	CV ISS
Total Study Participants	119	87	18	58	**282**	--	--	--
Total Randomized (b) (4)	119	87	18	--	**224**	--	ISS-ALL	--
Total Randomized – DB Study Only	119	87	--	--	**206**	ISE-DB	ISS-DB-SAF	ISS-DB
Total Entered OLE – Received ≥ 1 dose of FEN by interim cutoff date	110	48	16	58	**232**[b]	--	LTS-ALL	LTS
Total entered OLE from completed DB Study; received ≥ 1 dose by interim cutoff date	110	48	--	--	**158**		LTS-DB	LTS-DB
Total entered OLE (b) (4) – Received ≥ 1 dose of FEN by interim cutoff date	110	48	16	--	**174**	--	LTS	--
Total unique FEN patients (b) (4) – Received ≥ 1 dose of FEN by cutoff date of 120-day safety update	110	83	16	121	**341**[c]		120-day safety update	

Source: ADSL (ISS), ADSL (120-day)
Abbreviations: CV=cardiovascular; DB=double-blind; LTS=long-term safety; OLE=open-label extension.
a - (b) (4)
b - Equivalent to the Study 1503 Safety Population in ISS.
c – Includes all patients in Studies 1, 1504-C1, 1504-C2, 1503, and the open-label exposure for (b) (4) subjects up to the cutoff for the 120-day safety update

Table 38: Duration of Exposure, All Populations

	Study 1504 C1 Transition Period[1] FEN 0.2 mg (N=15)	Double-blind Studies[2] FEN Any Dose (N=122)	Double-blind Studies[3] FEN Any Dose (incl PBO dur. transition) (N=206)	Study 1503[4] FEN Any Dose (N=174)	FEN Treated Patients (not incl 120-day update)[5] (N=224)	All FEN Exposed Patients[6] (incl 120-day safety update) (N=341)
Summary Statistics						
n	15	122	206	174	224	341
Mean (days)	142.1	109.8	71.2	311.9	317.3	619.1
SD	56.90	23.51	50.16	134.22	193.72	277.21
Median	169.0	113.5	109.0	320.5	326.5	639.0
Min, Max	0, 174	21, 145	0, 145	57, 634	0, 703	21,1199
Duration of Exposure						
<1 month	1 (6.7%)	2 (1.6%)	83 (40.3%)	0	22 (9.8%)	2 (0.6%)
1 to <3 months	2 (13.3%)	11 (9.0%)	14 (6.8%)	8 (4.6%)	12 (5.4%)	14 (4.1%)
3 to <6 months	12 (80.0%)	109 (89.3%)	109 (52.9%)	26 (14.9%)	32 (14.3%)	13 (3.8%)
6 to <12 months	0	0		75 (43.1%)	55 (24.6%)	28 (8.2%)
12 to <18 months	0	0		57 (32.8%)	73 (32.6%)	58 (17.0%)
18 to <24 months	0	0		8 (4.6%)	30 (13.4%)	88 (25.8%)
>=24 months	0	0		0	0	138 (40.5%)

[1] Transition period begins on day 16 and ends when a Patient discontinues treatment or enters study 1503. The exposure in Day 1 used for PK assessments is not included. 3 patients were not dosed in the transition period.
[2] Duration of exposure is the number of days from the date of first active FEN dose in Studies 1 or 1504 C2, to the date of last dose in the double-blind study. Placebo patients were not included although first exposure active FEN began during the transition period.
[3] Duration of exposure is the number of days from the date of first active FEN dose in Study 1 or Study 1504 C2, to the date of last dose in the double-blind study. For Placebo group patients, first exposure to FEN begins in the transition period of the core study.
[4] Duration of exposure is calculated from date of first dose in the OLE study to the last date of treatment or data cutoff date for this report, whichever is earlier.
[5] Total duration of active FEN exposure is based on exposure time in the core study plus time in study 1503. For Placebo group patients, first exposure begins in the transition period of the core study
[6] Total duration of active FEN exposure is based on exposure time in the core study plus time in study 1503. For patients in the placebo group, first exposure begins in the transition period of the core study. Includes patients from Studies 1, 1504-C1, and 1504-C2, and 1503 (b) (4).
Source: Table DX14 (revised, IR responses 19 FEB 2020 and 8 MAY 2020)

Table 39: Duration of Exposure According to Mean Daily Dose (LTS Population), Study 1503

Duration (Months)	>0 to 0.2 mg/kg/day (n)	>0.2 to <0.4 mg/kg/day (n)	0.4 to 0.6 mg/kg/day (n)	>0.6 to 0.8 mg/kg/day (n)	Total n (%)
Total n (%)	**29 (13%)**	**66 (28%)**	**76 (33%)**	**61 (26%)**	**232 (100%)**
>1 to ≤ 6	11	30	17	6	64 (28%)
>6 to ≤ 12	15	29	39	24	107 (46%)
>12 to ≤ 18	2	6	20	25	53 (23%)
>18 to ≤ 24	1	1	0	6	8 (3%)

a – Mean daily dose calculated over patient's treatment period in Study 1503
Source: ISS, Table 9

8.2.2. Relevant characteristics of the safety population:

Baseline demographics for subjects in the ISS-DB treatment groups were balanced as seen in Table 40. Slightly more than 25% of randomized patients were <6 years old (26.2% for the Pooled DB FEN group and 27.4% for the combined placebo group). The majority of patients were male (57.1% and 54.1% in the placebo and pooled FEN groups, respectively. A total of 47.5% of patients in the pooled FEN group and 40.5% of patients in the placebo group were enrolled in the US.

Table 40: Baseline Demographics, Safety populations

	Double-Blind Safety Population					Open Label Safety Population
	Pooled Placebo (N=84)	FEN 0.2 mg (N=39)	FEN 0.8 mg (N=40)	FEN 0.5 mg* (N=43)	Pooled DB FEN (N=122)	All FEN in OLE (N=232)
Age (years)						
Mean (SD)	9.3 (5.04)	9.0 (4.52)	8.8 (4.41)	8.8 (4.56)	8.9 (4.46)	9.1 (4.71)
Min, Max	2, 19	2, 17	2, 18	2, 18	2, 18	2, 19
Age Group, n (%)						
<6 Years	23 (27.4%)	9 (23.1%)	11 (27.5%)	12 (27.9%)	32 (26.2%)	65 (28%)
≥6 Years	61 (72.6%)	30 (76.9%)	29 (72.5%)	31 (72.1%)	90 (73.8%)	167 (72%)
Sex						
Male	48 (57.1%)	22 (56.4%)	21 (52.5%)	23 (53.5%)	66 (54.1%)	128 (55.2%)
Female	36 (42.9%)	17 (43.6%)	19 (47.5%)	20 (46.5%)	56 (45.9%)	104 (44.8%)
Race*						
White	60 (71.4%)	33 (84.6%)	34 (85.0%)	23 (53.5%)	90 (73.8%)	172 (74.1%)
Black or African American	2 (2.4%)	0	0	1 (2.3%)	1 (0.8%)	1 (0.4%)
Asian	5 (6.0%)	2 (5.1%)	1 (2.5%)	2 (4.7%)	5 (4.1%)	9 (3.9%)
Native American	1 (1.2%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (0.9%)
Other	1 (1.2%)	0 (0.0%)	0 (0.0%)	3 (7.0%)	3 (2.5%)	13 (5.6%)
Not Reported	15 (17.9%)	3 (7.7%)	5 (12.5%)	14 (32.6%)	22 (18.0%)	35 (15.1%)
Ethnicity*						
Hispanic or Latino	11 (13.1%)	4 (10.3%)	3 (7.5%)	3 (7.0%)	10 (8.2%)	23 (9.9%)

	Double-Blind Safety Population					Open Label Safety Population
	Pooled Placebo (N=84)	FEN 0.2 mg (N=39)	FEN 0.8 mg (N=40)	FEN 0.5 mg* (N=43)	Pooled DB FEN (N=122)	All FEN in OLE (N=232)
Not Hispanic or Latino	51 (60.7%)	32 (82.1%)	32 (80.0%)	25 (58.1%)	89 (73.0%)	159 (68.5%)
Not Reported	19 (22.6%)	2 (5.1%)	4 (10.0%)	14 (32.6%)	20 (16.4%)	47 (20.3%)
Unknown	3 (3.6%)	1 (2.6%)	1 (2.5%)	1 (2.3%)	3 (2.5%)	3 (1.3%)
Region/Country						
Canada	4 (4.8%)	0 (0.0%)	1 (2.5%)	4 (9.3%)	5 (4.1%)	9 (3.9%)
United States	34 (40.5%)	24 (61.5%)	23 (57.5%)	11 (25.6%)	58 (47.5%)	102 (44.0%)
Europe	46 (54.8%)	14 (35.9%)	15 (37.5%)	28 (65.1%)	57 (46.7%)	115 (50.0%)
Australia	0 (0.0%)	1 (2.6%)	1 (2.5%)	0 (0.0%)	2 (1.6%)	6 (2.6%)
Baseline Height (m)						
Mean	1.302	1.312	1.285	1.307	1.301	1.32
SD	0.2391	0.2235	0.2041	0.2354	0.2202	0.233
Median	1.310	1.325	1.295	1.320	1.320	1.33
Baseline Weight (kg)						
Mean	34.053	35.116	31.789	31.321	32.688	33.51
SD	18.9118	19.5689	13.4708	14.8459	16.0650	17.295
Median	28.530	29.620	28.305	27.940	28.325	28.71
Baseline BMI (kg/m^2)						
Mean	18.578	19.324	18.475	17.319	18.331	17.92
SD	4.4163	5.6875	3.5023	2.7146	4.1504	4.184
Median	17.560	17.240	18.025	16.580	17.340	17.02

*0.5 mg/kg/day is not an intermediate dose.
Source: ISS ADSL, Study 1503 ADSL

8.2.3. Adequacy of the safety database

Based on the characteristics in Table 40, the development program provides generally adequate representation across the DS population; however, the studies enrolled only 4 black patients and only 15 Asian patients. The course of DS, a genetic disease, is not known to differ importantly in these minority populations. It is unclear if race or ethnicity are factors that would predispose these populations to fenfluramine-induced VHD or PAH; however, neither were reported as factors in the published studies of fenfluramine-induced VHD and PAH. Given the rarity of these diseases, the patient demographic exposure seems adequately diverse and generalizable to the to-be-marked U.S. patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was performed by Jumpstart, and no significant issues were identified.

Routine clinical safety evaluations were scheduled (and generally occurred) at the following

timepoints:

- Study 1 (98-day treatment period): On-treatment visits were scheduled on Days 15, 29, 43, and 71, with additional safety telephone calls on Days 4, 29, and 85. In addition, an end-of-treatment visit was scheduled at Day 106.

- Study 1504-C2 (105-day treatment period): On-treatment visits were scheduled on Days 15, 22, 50, and 78, with additional telephone calls on Days 8, 36, 64, and 92. Patients were to return for an end-of-treatment visit on Day 106.

8.3.2. Categorization of Adverse Events

The Applicant used standard procedures to collect and analyze adverse event data. Adverse events were recorded at all subject visits, and subjects were to be monitored for adverse events through 28 days after the last dose of test drug, as well as an ECHO follow-up 3-6 months after the last dose of study drug. Investigators were asked to decide on causality and to provide their opinion on intensity (mild, moderate, severe) of each AE.

The standard definition of serious adverse event was used in the development program. Treatment emergent adverse events (TEAEs) were defined as *"as any AE that, based on start date information, occurred after the first intake of study treatment."* Expected seizure types were not to be recorded as adverse events; however, changes in the pattern or severity of seizures were to be considered adverse events. Status epilepticus and seizure clusters were also to be recorded as AEs. Clinically significant abnormalities in clinical laboratory tests were to be documented as adverse events.

Multiple occurrences of adverse events were counted once, per specific Medical Dictionary for Regulatory Activities (MedDRA) preferred term. In Study 1503, the open-label extension trial, AEs that were continuing from the original trial were carried over as medical history and not classified as adverse events unless they worsened. MedDRA (version 19.0) was used for coding of adverse events for all the clinical studies.

As noted above, the ADAE.xpt datafile was reviewed for accuracy of translation from verbatim to preferred term through manual review.

Characterization of seizures as AEs in an efficacy trial of a seizure treatment drug is at times complicated by reporting of specific types of seizures. As the incidence of any type of seizure is most important when assessing seizures as AEs, all subtypes of seizures were recoded as "Seizure", except for status epilepticus. The preferred terms "Atonic seizures", "Change in seizure presentation", "Clonic convulsion", "Febrile convulsion", "Generalised tonic-clonic seizure", "Myoclonic epilepsy", "Myoclonus", "Partial seizures", "Petit mal epilepsy", "Seizure cluster", and "Tonic convulsion" were included in the "Seizure" grouping. "Somnolence," "Sedation," and "Lethargy" were combined in a grouping, as were "Fatigue", "Asthenia", and "Malaise". See Table 41 below for specific changes and revised groupings.

Table 41: Recoded AE Codes

Original Coded Preferred Term(s)	Recoded Term
Abdominal pain upper, Abdominal discomfort	Abdominal pain
Blood pressure diastolic increased, Blood pressure systolic increased	Blood pressure increased
Otitis media acute, Otitis media	Ear infection
Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test increased	Elevated transaminase
Viral gastroenteritis	Gastroenteritis
Initial insomnia, Middle insomnia	Insomnia
Urticaria, Rash erythematous, Rash papular, Rash maculo-papular, Rash generalized, Rash macular	Rash
Atonic seizures, Change in seizure presentation, Clonic convulsion, Epilepsy, Febrile convulsion, Generalised tonic-clonic seizure, Myoclonic epilepsy, Myoclonus, Partial seizures, Petit mal epilepsy, Seizure cluster, Tonic convulsion	Seizures
Upper respiratory tract infection viral	Upper Respiratory Tract Infection

As seen in Table 42 below, a number of seizures were omitted through incomplete translation from the verbatim term to the preferred term. These events were added to the dataset.

Table 42: Additional Seizures Identified in AE Dataset, ISS

Dictionary-Derived Term	Reported Term for the Adverse Event	Add
Skin abrasion	FOREHEAD ABRASION DUE TO SEIZURE	Seizure
Pneumonia aspiration	PNEUMONIA DUE TO INHALATION DURING SEIZURES	Seizure
Fall	FALL FROM SEIZURE	Seizure
Fall	FALL - DURING GTC POST STUDY VISIT	Seizure
Lip injury	BIT LIP DURING SEIZURE	Seizure
Postictal headache	HEAD ACHE AFTER 4 GTKA SEIZURES	Seizure
Fall	SEIZURE ACCIDENT - IN THE SETTING OF A SEIZURE ON 02JAN2016, SHE FELL OUT OF HER CHAIR	Seizure
Drooling	DROOLING POST SEIZURE	Seizure
Drug dose omission	NON-COMPLIANCE WITH SEIZURE MEDICATION CAUSING FREQUENT SEIZURE, SEIZURE MEDICATION WAS NOT GIVEN.	Seizure
Laceration	VERY MILD HEAD INJURY RESULTING IN SMALL LACERATION TO HEAD. CHILD BUMPED HEAD ON WOODEN TABLE DURING A SEIZURE. NO TREATMENT REQUIRED.	Seizure

The Applicant designated adverse events of special interest (AESI), and these received specific attention. The initial list of AESI is as follows:

Adverse Events of Special Interest (AESI) Specified in the Protocols for Studies 1 and 1504-C2
CV/Respiratory
1. Chest pain – any pain in sternal area that is described for example as crushing, burning, sharp, stabbing or dull.
2. Dyspnea/shortness of breath – any signs of difficult or labored breathing unrelated to a previous medical condition that has not worsened.
3. Persistent cough – longer than 4 weeks without a confirmed identified pathogen (or any other persistent cough that the investigator feels is suspicious).
4. Increase in blood pressure >30% from Screening blood pressure or a systolic pressure ≥140 mmHg after repeated measures during one visit. Blood pressure should be repeated at appropriate times within the visit.
5. Jugular venous distention- visible bulging of the external jugular veins on either side of the neck
6. New onset heart murmur
7. Pulmonary rales – an abnormal respiratory sound heard during auscultation of the lungs, which is also described as a crackle.
8. Tachycardia – a persistent HR >30% above the screening value and unrelated to exercise, exertion or anxiety. Heart rate should be repeated at appropriate times within the visit.
9. Signs that could indicate right ventricular failure: a. Peripheral edema, b. Ascites, c. Syncope, d. Decompensated right ventricular failure – symptoms include shortness of breath, frequent coughing especially when lying flat, abdominal swelling and pain, dizziness, fainting, and fatigue
10. Signs on ECHO indicative of potential valvulopathy a. valve regurgitation (aortic or mitral) b. moderate or severe valve regurgitation (tricuspid or pulmonary) c. Mean Mitral valve gradient ≥ 4 mmHg d. Mean Aortic valve gradient ≥ 15 mmHg e. Mean Tricuspid valve gradient ≥ 4 mmHg f. Peak Pulmonary valve gradient ≥ 21 mmHg
11. Signs on ECHO indicative of pulmonary hypertension a. Tricuspid Regurgitation Jet velocity > 2.8 msec with or without the following findings OR b. One of the following findings in the absence of being able to measure Tricuspid Regurgitation Jet velocity: i. Change in right ventricle/left ventricle basal diameter ratio > 1.0 ii. Right ventricular acceleration time < 100 msec iii. Dilatation of the inferior caval vein (diameter>21 mm and <50% inspiratory decrease) and/or right atrium iv. Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole v. Early diastolic pulmonary regurgitation velocity > 2.2 m/sec vi. Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score – 2

Adverse Events of Special Interest (AESI) Specified in the Protocols for Studies 1 and 1504-C2
Metabolic/Endocrine
1. Elevated prolactin level ≥2x above the upper limit of normal (ULN)
2. Galactorrhea
3. Gynecomastia
4. Increase in fasting serum blood glucose ≥2x ULN
5. Hypoglycemia – serum blood glucose more than 20% below the glucose level on Study Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)
Neuropsychiatric
1. Serotonin syndrome (At least 3 of following symptoms must be present: Agitation, restlessness, confusion, both increased HR and blood pressure, dilated pupils, muscle twitching, muscle rigidity, hyperhidrosis, diarrhea, headache, shivering, tremors, both nausea and vomiting)
2. Hallucinations
3. Psychosis
4. Euphoria
5. Mood disorders: depression and anxiety if they rise to a level of a disorder
6. Suicidal thoughts, ideation or gestures
Genitourinary
1. Priapism

Due to frequency of AEs and overlap with other clinical disorders, a subset of AESIs were to be summarized in line listings, rather than as AESIs: cardiovascular/respiratory items, including discontinuation of the reporting of ECHOs with trace mitral regurgitation as AESIs; serotonin syndrome; hallucinations, psychosis, euphoria, mood disorders; galactorrhea, gynecomastia, priapism; and fasting serum blood glucose ≥2×ULN. Other events that were to be summarized included weight loss/appetite suppression; somnolence, sedation, fatigue, and lethargy; seizures; and behavioral abnormalities.

8.3.3. Routine Clinical Tests

Assessments of vital signs and laboratory monitoring were performed at screening, randomization and multiple timepoints throughout both trials. Laboratory monitoring included assessments of the following:

- Chemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, and uric acid.
- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

- Urinalysis

Missing data were sparse. There was no indication that laboratory data were obtained in the fasting state. The Applicant evaluated laboratory values based on the Common Terminology Criteria for Adverse Events grading scheme (version 4.03).

8.4. Safety Results

8.4.1. Deaths

Four deaths have been reported during the development program, one of which occurred during the controlled trials. All four deaths were attributed to SUDEP. One patient death (Subject (b) (6)) occurred on Study Day 89 in Study 1503 (Day 227 of overall study participation). The second patient death (Subject (b) (6)) occurred on Study Day 69 (b) (4) (b) (4). The third death (Subject (b) (6)) occurred after the ISS interim database cutoff on Study Day 443 in Study 1503 (Day 567 of overall study participation) but was included in the resubmission. The fourth death, also SUDEP, was reported on January 9, 2020 in a patient (# (b) (6)) in Study 1503. Follow up on this last death is ongoing as of the time of submission of the 120 Day Safety Update.

Reviewer's comment: Patients these studies were often ill, with complex, chronic multisystem diseases and complicated courses. It is not possible to attribute the deaths to fenfluramine, but it is not possible to be certain that the drug did not contribute in some way. The reported or suspected cause of death in all 4 patients is SUDEP, which is common in the DS population (9.32/1000 person-years), more so than in the epilepsy population at large (1.5-5.1/1000 person-years).[12] Therefore, it would not seem appropriate to attribute these deaths to the investigational drug.

8.4.2. Serious Adverse Events

Controlled Trials

A total of 33 serious TEAEs occurred in 21 patients during the titration and maintenance periods in Studies 1 and 1504-C2 (Table 43). The incidence of serious TEAEs was similar in patients in the pooled FEN group compared to placebo. Overall, 11 patients (9.0%) in the pooled FEN treatment group and 10 patients (11.9%) in the combined placebo group reported at least 1 serious TEAE. The most frequently reported serious TEAEs in the pooled FEN group and the combined placebo group occurred in the Nervous System Disorders SOC (7 [6.3%] patients in the pooled FEN group and 7 [8.3%] patients in the combined placebo group). The serious TEAE that occurred most frequently in the pooled FEN group was status epilepticus (4 [3.3%]). Three patients in the pooled FEN group experienced a serious TEAE of somnolence (3 [2.5%]). All other serious TEAEs in the pooled FEN group occurred in a single patient only (seizure, lower respiratory tract infection, adverse drug reaction, decreased appetite, diarrhea, hypoxia, osteochondritis, and weight decreased). The most frequently occurring serious TEAE in the placebo group was seizure (6 [7.1%]). Other serious TEAEs that occurred in more than one

patient in the placebo group included status epilepticus and pneumonia (2 patients each [2.4%]). The rest of the serious TEAEs in the placebo group occurred in a single patient (Lower respiratory tract infection, Abdominal pain, Head injury, and Pyrexia).

Reviewer's Comments: The types and frequencies of TEAEs reported in Studies 1 and 1504-C2 are similar to those seen in other trials of refractory epilepsy in pediatric patients.

Table 43: Serious Treatment-Emergent Adverse Events, Controlled Safety Population

	Pooled Placebo (N=84)		Study 1				Study 1504-C2		Pooled FEN (N=122)		Overall (N=206)		RR	Δ Risk (%)
			FEN 0.2 mg/kg (N=39)		FEN 0.8 mg/kg (N=40)		FEN 0.5 mg/kg* (N=43)							
	n	%	n	%	n	%	n	%	n	%	n	%		
Any SAE	**10**	**11.9%**	**3**	**7.7%**	**3**	**7.5%**	**5**	**11.6%**	**11**	**9.0%**	**21**	**10.2%**		
Seizure	6	7.1%	0		1	2.5%	0		1	0.8%	7	3.4%	0.1	-6
Status epilepticus	2	2.4%	1	2.6%	0		3	7.0%	4	3.3%	6	2.9%	1.4	1
Somnolence	0		0		2	5.0%	1	2.3%	3	2.5%	3	1.5%	4.8	2
Lower respiratory tract infection	1	1.2%	1	2.6%	0		0		1	0.8%	2	1.0%	0.7	0
Pneumonia	2	2.4%	0		0		0		0		2	1.0%	0.1	-2
Abdominal pain	1	1.2%	0		0		0		0		1	0.5%	0.2	-1
Adverse drug reaction	0		0		1	2.5%	0		1	0.8%	1	0.5%	2.1	1
Decreased appetite	0		0		1	2.5%	0		1	0.8%	1	0.5%	2.1	1
Diarrhea	0		0		1	2.5%	0		1	0.8%	1	0.5%	2.1	1
Head injury	1	1.2%	0		0		0		0		1	0.5%	0.2	-1
Hypoxia	0		1	2.6%	0		0		1	0.8%	1	0.5%	2.1	1
Osteochondritis	0		0		0		1	2.3%	1	0.8%	1	0.5%	2.1	1
Pyrexia	1	1.2%	0		0		0		0		1	0.5%	0.2	-1
Weight decreased	0		0		1	2.5%	0		1	0.8%	1	0.5%	2.1	1

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADAE (JMP, MAED)

Uncontrolled Safety Data

A total of 160 serious TEAEs occurred in 86 patients in the uncontrolled safety population (Table 44). Nervous system and infectious serious adverse TEAEs occurred most frequently (15.1% and 10.0%, respectively). The most frequently reported serious TEAE in the uncontrolled patient population was seizures, which occurred in 38 (11.5%) patients. Other frequently reported serious TEAEs were status epilepticus (4.5%), pneumonia (3%), and viral infection or gastroenteritis (1.2% each). All other serious TEAEs occurred in <1% of the uncontrolled patient population.

Table 44: Serious Treatment-Emergent Adverse Events, Uncontrolled Population

	All uncontrolled FEN (N=331)	
	n	%
Any SE	**86**	**26.0%**
Cardiac Disorders	**2**	**0.6%**
Atrioventricular Block Second Degree	1	0.3%
Tachycardia	1	0.3%
Gastrointestinal Disorders	**6**	**1.8%**
Constipation	1	0.3%
Diarrhea Hemorrhagic	1	0.3%
Dysphagia	1	0.3%
Enterovesical Fistula	1	0.3%
Hematemesis	1	0.3%
Lip Disorder	1	0.3%
Tooth Disorder	1	0.3%
General Disorders and Administration Site Conditions	**5**	**1.5%**
Abasia	1	0.3%
Adverse Drug Reaction	1	0.3%
Hypothermia	1	0.3%
Sudden Unexplained Death In Epilepsy	2	0.6%
Infections and Infestations	**33**	**10.0%**
Bronchitis	1	0.3%
Cellulitis	2	0.6%
Ear Infection	1	0.3%
Gastroenteritis	4	1.2%
Infectious Mononucleosis	1	0.3%
Influenza	6	1.8%
Lower Respiratory Tract Infection	3	0.9%
Lung Infection	1	0.3%
Pharyngitis	1	0.3%
Pneumonia	10	3.0%
Postoperative Wound Infection	1	0.3%
Rhinovirus Infection	1	0.3%
Sepsis	1	0.3%
Upper Respiratory Tract Infection	2	0.6%

	All uncontrolled FEN (N=331)	
	n	%
Viral Infection	4	1.2%
Injury, Poisoning and Procedural Complications	**7**	**2.1%**
Cervical Vertebral Fracture	1	0.3%
Concussion	1	0.3%
Drug Dose Omission	1	0.3%
Extremity Fracture	1	0.3%
Fall	1	0.3%
Foreign Body Aspiration	1	0.3%
Head Injury	2	0.6%
Metabolism and Nutrition Disorders	**3**	**0.9%**
Dehydration	1	0.3%
Feeding Intolerance	1	0.3%
Hyponatremia	1	0.3%
Musculoskeletal and Connective Tissue Disorders	**2**	**0.6%**
Aneurysmal Bone Cyst	1	0.3%
Foot Deformity	1	0.3%
Nervous System Disorders	**50**	**15.1%**
Cerebral Hemorrhage	1	0.3%
Encephalopathy	1	0.3%
Hyperkinesia	2	0.6%
Movement Disorder	2	0.6%
Seizure	38	11.5%
Status Epilepticus	15	4.5%
Psychiatric Disorders	**2**	**0.6%**
Agitation	1	0.3%
Insomnia	1	0.3%
Tic	1	0.3%
Respiratory, Thoracic and Mediastinal Disorders	**4**	**1.2%**
Acute Respiratory Distress Syndrome	1	0.3%
Apnea	1	0.3%
Pneumonia Aspiration	1	0.3%
Respiratory Distress	2	0.6%
Skin and Subcutaneous Tissue Disorders	**1**	**0.3%**
Rash	1	0.3%

Source: ADAE (from ISS and 120-Day Safety Update), revised and analyzed in JMP

Reviewer's Comments: The most frequently reported serious TEAEs in the uncontrolled population were seizures (of any type) and status epilepticus, both of which are frequently reported in this population and are likely related to the underlying diagnosis of DS. Serious pneumonia was also reported in the controlled safety population as well in the uncontrolled population. Serious events of somnolence and decreased appetite were not seen in the uncontrolled population. Lower frequency serious TEAEs seem generally

consistent with expected frequencies in the patient population.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Controlled Trials

As seen in Table 45 below, 13 patients (6.3%) discontinued early because of adverse events during the titration and maintenance periods of both studies, 7 (5.9%) in Study 1 and 6 (6.9%) in Study 1504-C2. This rate differs slightly from that reported by the Applicant in the ISS and in the CSRs for both studies. The data used to calculate the discontinuation rate due to AEs was derived from the ADAM datasets for each study, as well as listings from the CSR for each study and confirmed on review of the patients' disposition CRFs. The differences between the FDA and Applicant's disposition analyses are described above in Section 6.1.2 and Section 6.2.2 (Patient Disposition).

Table 45: Randomized Subjects, Disposition by Arm, Controlled Safety Population

	Placebo		FEN 0.2 mg/kg		FEN 0.8 mg/kg		FEN 0.5 mg/kg*		Pool FEN		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Completed	77	91.7%	39	100%	34	85%	36	83.7%	109	89.3%	186	90.3%
Early termination	7	8.3%	0		6	15%	7	16.3%	13	10.7%	20	9.7%
Adverse Event	**5**	**6.0%**	**0**		**5**	**12.5%**	**3**	**7.0%**	**8**	**6.6%**	**13**	**6.3%**
Lack of Efficacy	1	1.2%	0		0		1	2.3%	1	0.8%	2	1.0%
Other	0		0		0		1	2.3%	1	0.8%	1	0.5%
Physician Decision	0		0		0		1	2.3%	1	0.8%	1	0.5%
Withdrawal by Subject	1	1.2%	0		1	2.5%	1	2.3%	2	1.6%	3	1.5%

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADSL, ISS, modified by reviewer based on information in CRFs and narratives

These 13 patients experienced 19 adverse events leading to discontinuation, with 3 patients experiencing more than one AE (Table 46). AEs leading to discontinuation which occurred in more than one patient included seizure (n=6, 2.9%), somnolence/lethargy (n=3, 1.5%), and decreased appetite (n=2, 1%). The rest of the events occurred in one patient each. Nervous system events leading to discontinuation were notable, with 11 events occurring in 10 patients. Eight patients (7.1%) in the pooled FEN group and 5 patients (6%) in the placebo group exited the studies early during titration or maintenance due to an adverse event. All but one patient who discontinued participation due to an adverse event did so during the maintenance period. The only patient who exited the study early during the titration period because of an AE,

developed a rash (FEN 0.8 mg) on day 11 of treatment.

Table 46: Treatment-Emergent AEs Leading to Discontinuation, Controlled Safety Population

MedDRA System Organ Class/ Preferred Term	Placebo (N=84)	FEN 0.2 mg/kg (N=39)	FEN 0.8 mg/kg (N=40)	FEN 0.5 mg/kg* (N=43)	Pooled FEN (N=122)	All patients (N=206)
Any TEAE	**5 (6.0%)**	**0**	**5 (12.5%)**	**3 (7.0%)**	**8 (7.1%)**	**13 (6.3%)**
Gastrointestinal disorders	**0**	**0**	**1 (2.5%)**	**0**	**1 (0.8%)**	**1 (0.5%)**
Diarrhea	0	0	1 (2.5%)	0	1 (0.8%)	1 (0.5%)
Investigations	0	0	1 (2.5%)	0	1 (0.8%)	1 (0.5%)
Weight decreased	0	0	1 (2.5%)	0	1 (0.8%)	1 (0.5%)
Metabolism and nutrition disorders	**0**	**0**	**1 (2.5%)**	**1 (2.3%)**	**2 (1.6%)**	**2 (1.0%)**
Decreased appetite	0	0	1 (2.5%)	1 (2.3%)	2 (1.6%)	2 (1.0%)
Nervous system disorders	**5 (6.0%)**	**0**	**3 (7.5%)**	**3 (7.0%)**	**6 (5.4%)**	**10 (4.9%)**
Ataxia	0	0	0	1 (2.3%)	1 (0.8%)	1 (0.5%)
Dysarthria	0	0	0	1 (2.3%)	1 (0.8%)	1 (0.5%)
Seizure	5 (6.0%)	0	0	1 (2.3%)	1 (0.8%)	6 (2.9%)
Somnolence/Lethargy			3 (7.5%)		3 (2.7%)	3 (1.5%)
Psychiatric disorders	**0**	**0**	**1 (2.5%)**	**0**	**1 (0.8%)**	**1 (0.5%)**
Aggression	0	0	1 (2.5%)	0	1 (0.8%)	1 (0.5%)
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (2.5%)**	**0**	**1 (0.8%)**	**1 (0.5%)**
Rash	0	0	1 (2.5%)	0	1 (0.8%)	1 (0.5%)

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ISS ADAE and ADSL with revisions

Reviewer's Comments: As noted above, the discontinuation rate due to AEs in my analysis differ from that in the Applicant's analyses, as several discontinuations were deemed due to other reasons besides AEs in the overall analysis but were associated with adverse events in the narratives.

There were similar incidences of patients who discontinued participation due to AEs in the all FEN (7.1% and placebo (6%) group, with the highest incidence occurring in the 0.8 mg/kg/day group (12.5%). Seizures were most frequent in the placebo group (6%) and somnolence (2.7%) in the all FEN group.

In general, the TEAEs leading to discontinuation were consistent with AEs seen in similar circumstances in other AED studies.

8.4.4. Significant Adverse Events

A total of 8 patients in the controlled trials experienced 11 TEAEs that were adjudicated as

severe. Two patients experienced 2 severe TEAEs each while the rest of the patients each experienced a single severe TEAE. The only severe TEAE that occurred in more than one patient was status epilepticus, which was reported in two patients. The severe TEAEs that occurred in one patient each were adverse drug reaction, aggression, hypoxia, lower limb fracture, sleep apnea syndrome, seizure, somnolence, and skin lesion. Only one of these events (somnolence) led to drug discontinuation.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Controlled population

A total of 822 treatment emergent adverse events (TEAEs) occurred in 179/206 (87%) patients in the pooled controlled safety database. Overall, TEAEs were more common in patients taking any dose of FEN (114, 93%) than taking placebo (65, 77%) during the titration and maintenance periods. Overall TEAE rates were similar in the 3 dose groups: 0.2 mg – 92%, 0.5 mg – 95%, and 0.8 mg – 92%. A summary of the percentages of subjects with TEAEs that occurred in at least 2% of patients in the any FEN group are presented in Table 47 below.

These TEAEs can be divided into several broad categories, and some of the interrelations among AEs within categories suggest that the adverse events are fenfluramine-related, although there were no obvious dose-responses:

- Decreased appetite (37% vs. 8%) and weight decreased (8% vs. 1%) in the fenfluramine and placebo groups, respectively. There was no clear dose response for these findings, with greater frequency of weight decreased in 0.2 mg group compared to the 0.5 and 0.8 mg group, and greatest frequency of decreased appetite in the 0.5 mg group. Decreased appetite is notable because of the overall frequency of the event and the high-risk difference (28.6%). See Section 8.5.2 for further discussion of appetite- and weight-related effects of FEN.
- Other gastrointestinal events, including diarrhea, constipation, drooling/salivary hypersecretion, and gastroenteritis. Diarrhea is notable because of the risk difference (17%), although there was no apparent dose-response.
- Central nervous system events. These include several groupings of AEs (fatigue/malaise/asthenia, somnolence/lethargy/sedation, ataxia/balance disorder/gait disturbance), as well as abnormal behavior, tremor, status epilepticus, aggression, and hypotonia. None of these events exhibited a dose response.
- Infections with imbalances in rhinitis, urinary tract infections, and bronchitis. However, incidences of other infections (nasopharyngitis, influenza, pneumonia) were higher in the placebo group, making any interpretation difficult.
- Rash was more frequently seen in the any FEN group (7%) as compared to placebo (4%); however, only one patient discontinued participation due to rash.
- Echocardiogram abnormal – see Section 8.5.1 below for discussion of abnormal echocardiogram AEs.

Reviewer's comment:
In general, adverse events were more frequently seen in patients in the FEN groups than in the placebo group; however, there were no clear dose responses in any frequently-reported TEAE.

There are differences between my results and the Applicant's, primarily due to grouping of similar AEs, additions of uncoded AEs found in review of the verbatim terms, and some changes to preferred terms based on verbatim terms. These differences are described in Sections 8.1 and 8.3.2 above.

Please see Section 8.5.2 for discussion of decreased appetite and weight loss TEAEs.

Seizures reported as adverse events occurred more frequently in patients in the combined placebo group (20.2%) as compared to the pooled FEN group (8.2%). However, status epilepticus was reported in 11.4% of patients in the 0.5 mg group, 4.9% of the pooled FEN group and 2.4% of the combined placebo group. The significance of this imbalance is unclear.

Table 47: All Treatment-Emergent Adverse Events (≥2% FEN and Δ risk ≥2%), Controlled Safety Population

	Pooled Placebo (N = 84)		FEN 0.2 mg (N=39)		FEN 0.8 mg (N=40)		FEN 0.5 mg[#] (N=43)		Pooled DB FEN (N = 122)		Pooled FEN vs. Placebo		
	n	%	n	%	n	%	n	%	n	%	Δ risk	RR	OR
Any TEAE (Titration or Maintenance)	**65**	**77.4%**	**36**	**92.3%**	**37**	**92.5%**	**41**	**95.3%**	**114**	**93.4%**			
Gastrointestinal													
Decreased appetite	7	8.3%	9	23.1%	15	37.5%	21	48.8%	45	36.9%	28.6	4.43	6.43
Diarrhea	5	6.0%	12	30.8%	6	15.0%	10	23.3%	28	23.0%	17.0	3.86	4.71
Weight decreased	1	1.2%	5	12.8%	2	5.0%	3	7.0%	10	8.2%	7.0	6.89	7.41
Constipation	0		1	2.6%	4	10.0%	3	7.0%	8	6.6%	6.6	11.75	12.55
Drooling/Salivary hypersecretion	0		5	12.8%	2	5.0%	1	2.3%	9	7.4%	7.4	13.1	14.1
Gastroenteritis	0		3	7.7%	1	2.5%	1	2.3%	5	4.1%	4.1	7.60	7.91
Nervous system													
Fatigue/Malaise/Asthenia	4	4.8%	6	15.4%	4	10.0%	13	30.2%	23	18.9%	14.1	3.96	4.65
Somnolence/Lethargy/Sedation	9	10.7%	10	25.6%	10	25.0%	10	23.3%	30	24.6%	13.9	2.30	2.72
Ataxia/Balance disorder/Gait disturbance	1	1.2%	4	10.3%	4	10.0%	3	7.0%	11	9.0%	7.8	7.57	8.23
Abnormal behavior	0		0		3	7.5%	4	9.3%	7	5.7%	5.7	10.37	10.97
Tremor	0		1	2.6%	1	2.5%	4	9.3%	6	4.9%	4.9	8.98	9.43
Status epilepticus	2	2.4%	1	2.6%	0		5	11.6%	6	4.9%	2.5	2.07	2.12
Aggression	0		1	2.6%	1	2.5%	1	2.3%	3	2.5%	2.5	4.84	4.95
Hypotonia	0		0		3	7.5%	0		3	2.5%	2.5	4.84	4.95
*Seizure**	17	20.2%	6	15.4%	3	7.5%	1	2.3%	10	8.2%	-12.0	0.41	0.35
Infections													
Rhinitis	2	2.4%	3	7.7%	1	2.5%	3	7.0%	7	5.7%	3.4	2.41	2.50
Urinary tract infection	0		2	5.1%	0		2	4.7%	4	3.3%	3.3	6.22	6.42
Bronchitis	1	1.2%	1	2.6%	0		4	9.3%	5	4.1%	2.9	3.44	3.55
Chills	0		0		2	5.0%	1	2.3%	3	2.5%	2.5	4.84	4.95
Other													
Rash	3	3.6%	3	7.7%	3	7.5%	2	4.7%	8	6.6%	3.0	1.84	1.90
*Echocardiogram abnormal***	5	6%	7	17.9%	9	22.5%	4	9.3%	20	16.4%	10.4	2.01	2.09
Urinary incontinence	0		2	5.1%	1	2.5%	0		3	2.5%	2.5	4.84	4.95

Source: ADAE (ISS), MAED/JMP

[#] 0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN

*Seizures as TEAEs were more frequently reported in the placebo group than in the FEN treatment groups. ** Abnormal echocardiogram TEAEs from transition period are included in the controlled study population, as these were based on ECHO results from Visit 12 (last visit of maintenance period). Other TEAEs reported during the transition period are included in the uncontrolled population.

Uncontrolled population

The uncontrolled safety population includes patients from the open-label safety study (Study 1503) and Study 1504-C1, a PK study in which all patients were taking FEN (±STP). A total of 331 patients are included in the uncontrolled safety population, which differs from the Applicant's inclusion of 330 patients (all from Study 1503). Of the 331 patients in the uncontrolled safety database used in this review, all but one were enrolled in Study 1503: 110 participated in Study 1, 83 in Study 1504-C2, 16 in Study 1504-C1 (b) (4). The final patient in the uncontrolled safety population is Subj# (b) (6) who experienced TEAEs in the FEN 0.2 mg/kg+CLB+VPA arm of Study 1504-C1 but did not enroll in Study 1503.

As seen in Table 48 below, 320 patients in the uncontrolled safety population experienced 2879 TEAEs, most of which occurred during Study 1503 (n=2657). The rest of the TEAEs in this dataset occurred during Study 1504-C1 (n=93 events) or during the transition periods of Studies 1 or 1504-C2 (n= 129 events). Most of these events were nonserious (n=2720). The most frequently reported TEAEs during the uncontrolled study periods were pyrexia (30%), nasopharyngitis (29%), seizure (29%), blood glucose decreased/hypoglycemia (28.4%), and decreased appetite (28%).

Most of the TEAEs reported in the uncontrolled population were mild (n=2357 in 313 patients, 95%). A total of 428 moderate TEAEs occurred in 167 patients (50%), and 32 patients (10%) experienced 65 severe TEAEs. The most frequently-reported severe TEAEs in the uncontrolled population were seizure (n=12, 3.6%), status epilepticus (5, 1.5%), and pneumonia (4, 1.2%).

Table 48: Treatment-Emergent Adverse Events (≥3%), Uncontrolled Safety Population

	All FEN Uncontrolled (N=331)	
Dictionary-derived term	**n**	**%**
Pyrexia	100	30.2%
Nasopharyngitis	97	29.3%
Blood glucose decreased/hypoglycemia	94	28.4%
Seizure	94	28.4%
Decreased appetite	81	24.5%
Echocardiogram abnormal	66	19.9%
Upper respiratory tract infection	66	19.9%
Diarrhea	62	18.7%
Gastroenteritis	54	16.3%
Ear infection	48	14.5%
Influenza	46	13.9%
Somnolence	36	10.9%
Vomiting	35	10.6%
Fatigue	32	9.7%
Rhinitis	30	9.1%
Abnormal behavior	28	8.5%
Weight decreased	27	8.2%

Dictionary-derived term	All FEN Uncontrolled (N=331)	
	n	%
Rash	26	7.9%
Cough	25	7.6%
Fall	24	7.3%
Blood pressure increased	23	6.9%
Viral infection	23	6.9%
Pharyngitis	22	6.6%
Gait disturbance	21	6.3%
Extremity fracture	20	6.0%
Pneumonia	19	5.7%
Constipation	18	5.4%
Status epilepticus	18	5.4%
Tremor	18	5.4%
Insomnia	16	4.8%
Aggression	15	4.5%
Oropharyngeal pain	15	4.5%
Bronchitis	14	4.2%
Nasal congestion	14	4.2%
Sinusitis	14	4.2%
Tachycardia	14	4.2%
Alopecia	13	3.9%
Contusion	13	3.9%
Laceration	13	3.9%
Respiratory tract infection	12	3.6%
Urinary tract infection	12	3.6%
Head injury	11	3.3%
Headache	11	3.3%
Rhinorrhea	11	3.3%
Conjunctivitis	10	3.0%

Source: ADAE (modified) 120-day safety update, JMP

Reviewer's Comments: Significant TEAEs are discussed in Section 8.5. In general, the TEAEs reported in the uncontrolled safety population also occurred during the blinded phases of Studies 1 and 1504-C2, and most of the frequently-reported TEAEs in the open-label extension study were seen frequently in the blinded phases, as well. Many of the TEAEs observed in the OLE study are seen fairly frequently in the general pediatric population (e.g., pyrexia, nasopharyngitis, upper respiratory tract infection, viral infection, gastroenteritis), may be considered due to the underlying condition (seizure, status epilepticus), or may be related to the drug (weight decreased).

8.4.6. Laboratory Findings

Hematology

Small decreases in the mean and median platelet counts from baseline were seen in all FEN groups compared to placebo, although the mean and median values remained within the normal reference ranges. The slight decrease in platelet count was not observed in the 0.5 mg/kg treatment group by Visit 10 (Day 71) but persisted in the 0.2 mg/kg and 0.8 mg/kg treatment groups (Table 49 and Table 50). At Visit 12, the mean platelet counts (10^9/L) had decreased slightly from baseline for the 0.2 and 0.8 mg/kg/day treatment groups and increased in the 0.5 mg/kg/day and placebo groups:

- FEN 0.2 mg/kg baseline mean (SD) 262.3 (71.8) to Visit 12 mean (SD) 236.6 (70.8)
- FEN 0.8 mg/kg baseline mean (SD) 266.9 (70.4) to Visit 12 mean (SD) 246.5 (64.5)
- FEN 0.5 mg/kg baseline mean (SD) 250.7 (85.36) to Visit 12 mean (SD) 268.5 (88.5)
- Placebo baseline mean (SD) 246.2 (92.1) to Visit 12 mean (SD) 264.6 (84.4)

During the blinded phase, 78 (64%) of patients in the pooled FEN group and 43 (51%) patients in the placebo group had a decreased in platelet count of ≥10% from baseline. When larger decreases in platelet counts of ≥25% from baseline were considered, they occurred in 37 (30%) of patients in the pooled FEN group and 15% of patients in the combined placebo group. There was no dose effect seen with decreased platelet counts in the FEN groups (Table 51).

In the controlled population, TEAEs of decreased platelet count were reported in 2 patients, and thrombocytopenia was reported in 1 patient. None of the TEAEs required treatment. The 2 TEAEs for decreased platelet count resolved. The TEAE for thrombocytopenia reported for Subject (b) (6) at Visit 12 during the double-blind treatment period did not report a resolution date; however, the platelet count for this patient was noted to be within the normal range at the next study visit (Month 1 in OLE study). Shift tables for platelets during the controlled trials demonstrated no significant difference between groups. Incidences of any patient experiencing a platelet count less than the lower limit of normal were similar amongst the treatment groups: 29%, 26%, 30%, 33% of patients in the placebo, 0.2 mg, 0.8 mg, and 0.5 mg groups, respectively. During the controlled trials, no patient had a platelet count <50 x 10^9/L, and 4 patients, one in each dose group, had at least one platelet count of <100 x 10^9/L.

Reviewer's Comments: The values in these analyses differ slightly from those provided by the Applicant, because a single outlier patient was excluded from the FDA analysis of platelet values. Subj (b) (6) (Study 1504-C2) had a platelet count of 233 x 10^9/L at his screening visit; however, his baseline platelet count was reported as 7 x 10^9/L at the baseline visit. A platelet count obtained at an unscheduled visit (day 15) was 282, and subsequent platelet counts for this patient were 156, 334, and 182 at visits 6, 10, and 12, respectively. It is presumed that the baseline value was an anomaly due to hemolysis of the sample. This patient's platelet test results significantly impacted the mean and median platelet counts for the 0.5 mg group (4671% change from baseline at the greatest) and therefore has been excluded from the analysis. Even with the exclusion of this patient from the analysis of the platelet counts, there was a mean increase in platelet counts from baseline in the FEN 0.5 mg group as compared

the mean decrease seen in the FEN 0.2 and 0.8 mg groups.

Decreases in the mean and median platelet counts from baseline observed in the FEN 0.2 and 0.8 mg treatment groups during the double-blind treatment periods persisted into the open-label treatment period, although mean and median values remained within the normal reference ranges. A similar slight decrease in platelet count was observed in the combined placebo group as these subjects began open-label treatment with FEN. The decrease in platelet count was not observed in the FEN 0.5 mg/kg treatment group during open-label treatment with ZX008. At Month 3 and Month 9, the mean platelet counts ($x10^9$/L) had remained decreased slightly from baseline:

- FEN 0.2 mg/kg baseline mean (SD) 264.8 (71.05) to Month 3 OLE 233.3 (50.02) and Month 9 OLE 250.2 (79.62)
- FEN 0.8 mg/kg baseline mean (SD) 271.2 (73.85) to Month 3 OLE 259.3 (83.49) and Month 9 OLE 244.0 (86.93)
- FEN 0.5 mg/kg baseline mean (SD) 229.4 (72.73) to Month 3 OLE 228.6 (63.34) and Month 9 OLE 239.5 (33.23)
- Placebo baseline mean (SD) 253.9 (93.15) to Month 3 OLE mean (SD) 247.2 (81.32) and Month 9 OLE 254.6 (72.2)

When change from baseline in platelet counts were assessed in the open label study, 122 (37%) and 330 patients had at least one platelet count that was decreased from baseline by ≥10%, and 70 (21%) patients had at least one platelet count that decreased from baseline by ≥25%. One patient reported a TEAE of thrombocytopenia during the OLE study. Subj (b) (6) reported a TEAE for thrombocytopenia (platelet count 137 x 10^9/L) at Day 30 of the OLE study. The patient's platelet count increased to 300 x 10^9/L at OLE Study Day 71 (reference range 181 to 521 x 10^9/L). A total of 73 patients (22%) had at least on platelet count less than the lower limit of normal during the OLE study.

Reviewer's comment: Persistent decreases in mean and median platelet counts from baseline were observed through the controlled studies in patients in the 0.2 and 0.8 mg/kg/day groups, and transiently in the 0.5 mg/kg/day group (mean and median platelet counts were greater than baseline in the 0.5 mg/kg/day group by visit 10). Mean and median platelet counts increased from baseline in patients in the combined placebo group. As seen in Table 51 below, the incidence of patients with ≥10% and ≥25% decrease from baseline in platelets was greater in the FEN groups than in the combined placebo group, although there was no clear dose effect. Incidences of patients with platelet counts less the LLN in all groups were similar. The magnitude of these effects was small and the lack of a clear dose effect of fenfluramine on platelet counts makes these findings of minimal clinical concern.

In the controlled trials and in the uncontrolled study, there were no other notable changes in hematology or chemistry.

Table 49: Observed Result for Platelets, Controlled Safety Population

	Visit 3 – Randomization				Visit 6				Visit 8				Visit 10				Visit 12			
	PBO	FEN			PBO	FEN			PBO	FEN			PBO	FEN			PBO	FEN		
		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*
N	81	37	40	39	77	39	38	36	73	35	35	33	73	34	34	34	76	37	36	38
Mean	246.2	262.3	266.9	256.28	256.2	239.9	252.6	231.2	257.9	241.2	246.9	240.8	258.4	248.9	243.5	256.3	264.6	236.6	246.5	268.5
SD	92.1	71.8	70.4	80.1	81.8	67.4	68.0	82.0	91.8	77.1	94.7	87.21	89.0	70.4	68.5	99.3	84.4	70.8	64.5	88.5
Min	47	126	147	121	115	127	137	89.00	104	114	79	111	112	116	133	110	99	88	140	119
Max	499	498	425	488	481	422	380	472	564	505	615	408	566	442	361	561	502	390	363	454

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADLB (ISS) in JMP clinical, excluding outlier

Table 50: Percent Change from Baseline for Platelets by Visit, Controlled Safety Population

	Visit 6				Visit 8				Visit 10				Visit 12			
	PBO	FEN			PBO	FEN			PBO	FEN			PBO	FEN		
		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*		0.2 mg	0.8 mg	0.5 mg*
N	74	37	37	33	70	33	34	33	70	33	33	31	73	35	35	35
Mean	10.1	-7.4	-4.3	-5.5	4.9	-8.1	-7.7	-5.5	6.4	-4.9	-9.0	0.6	13.6	-9.5	-7.2	6.7
SD	55.2	18.1	21.0	25.0	22.8	18.0	25.8	25.0	27.7	19.6	17.3	23.6	53.9	20.1	20.9	28.8
Min	-42.5	-36.2	-50.5	-61.3	-47.6	-49.3	-57.3	-61.3	-56.3	-35.8	-39.6	-38.9	-58.7	-56.7	-40.9	-33.9
Max	436.2	36.1	49.0	66.7	60	38.2	99.0	66.7	90.3	33.5	64.4	66.5	393.6	34.8	82.8	89.2

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADLB (ISS) in JMP clinical, excluding outlier

Table 51: Incidence of Patients ≥10% or ≥25% Decrease in Platelets from Baseline, Controlled Safety Population

Platelets	Placebo		FEN 0.2 mg/kg		FEN 0.8 mg/kg		FEN 0.5 mg/kg*	
	n	%	n	%	n	%	n	%
≥10% decrease	43	51.2%	26	66.7%	25	62.5%	27	62.8%
≥25% decrease	13	15.4%	14	35.9%	10	25%	13	30.2%

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADLB (ISS) in JMP clinical, excluding outlier

8.4.7. Vital Signs

Vital signs including height, body weight, body mass index, respiratory rate, heart rate, systolic and diastolic blood pressure, and body temperature were monitored during the clinical studies.

There were no clinically significant changes observed during the double-blind treatment period in the FEN treatment groups or the combined placebo group in heart rate, respiratory rate, or body temperature. No clinically significant changes were identified during the open-label extension study in height, heart rate, respiratory rate, or body temperature.

See Section 8.5.2 for discussion of effects of FEN on weight and BMI.

8.4.8. Electrocardiograms (ECGs)

There were no clinically significant findings in the analysis of ECGs during the controlled clinical trials. Please see Dr. Walker's review for a detailed review of the ECG analyses.

8.4.9. QT

A formal thorough QT study (Study 1603) was performed in the development program. No QT interval prolongation was reported at doses up to 4 times the maximum proposed dose in the labeling.

Electrocardiograms were obtained at intervals during Studies 1, 1504-C2, and 1503 and reviewed by a core lab (ERT). As per the ISS-CV safety report, *"no effects of ZX008 on cardiac repolarization or other electrocardiographic parameters. The ECG results reviewed for the studies comprising the overall clinical program showed no clinically significant treatment effect of ZX008. There was no effect on heart rate or evidence of an effect on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations and no effect on cardiac repolarization as measured by QT durations. There were no subjects considered to be clinically significant outliers by timepoint and categorical outlier analysis."*

Reviewer's Comments: No significant effects of Fintepla on QT or ECG were observed in the development program.

8.4.10. Immunogenicity

Immunogenicity testing was not performed.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Valvular Heart Disease and Pulmonary Arterial Hypertension

The primary impetus behind the removal of fenfluramine and dexfenfluramine from the market in 1997 was the previously unidentified association between these drugs and left-sided cardiac valvulopathy. Cardiac valve abnormalities were not identified in the clinical or nonclinical studies prior to approval of Pondimin®.[1,2]

In 1997, FDA received information about a case series of valvular heart disease identified in 24 women treated with phentermine and fenfluramine[1]. These women presented with symptomatic left- and/or right-sided valvular regurgitation, and 8 also had concurrent pulmonary hypertension. The valvular regurgitation in 5 (21%) of this original cohort was severe enough to require surgical intervention. Pathologic examination of the diseased valves revealed proliferative fibroblasts in a profuse extracellular matrix.

Because of the potential public health implications (an estimated 14 million prescriptions for fenfluramine or dexfenfluramine were written in 1997), FDA issued a public health advisory on July 8, 1997, seeking information about further cases of valvulopathy.[29] FDA eventually received 144 spontaneous reports of valvulopathy in patients taking either fenfluramine or dexfenfluramine with or without phentermine.[2] In order to exclude the relatively common occurrence of trace or mild mitral regurgitation (MR) or trace aortic regurgitation (AR), fenfluramine-related cardiac valvulopathy was defined as documented AR of mild or greater severity and/or documented MR of moderate or greater severity after exposure to these drugs (referred to as "FDA-defined valvulopathy").[30] Of the 144 spontaneous reports, 132 contained complete information. Of these, 113 (86%) met the above definition, and 87 (77%) patients were symptomatic. Twenty-seven (24%) patients required valve replacement surgery. The median age of the patients with valvulopathy in this publication was 44.

A subsequent meta-analysis of nine articles/studies was conducted to identify an estimated prevalence of cardiac valvular disease after exposure to fenfluramine or dexfenfluramine.[30] In this meta-analysis, a total of 3769 patients were exposed to the drugs and 5009 patients were not. The median age of the patients was 46. When FDA-defined valvulopathy was assessed, there was a pooled prevalence among patients treated >90 days of 12.0% compared to 5.9% in the untreated group (POR 2.2, 95% CI 1.7-2.7). However, in the group who were treated for less than 90 days, there was no difference in FDA defined valvulopathy prevalence between exposed and unexposed patients (6.7% vs 5.8% [POR 1.4, 95% CI 0.8-2.4]). Duration of use of fenfluramine was also demonstrated to be predictive of prevalence of mild or greater AR ($p<0.0001$ for trend), MR ($p=0.002$), and tricuspid regurgitation (TR) ($p<0.0001$) in a large

[29] Lumpkin MM. FDA public health advisory: Reports of valvular heart disease in patients receiving concomitant fenfluramine and phentermine. FDA Medical Bulletin, Volume 27, Issues 1-2
[30] Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. Am Heart J 2002; 144:1065-73.

observational study of 5743 fenfluramine users who underwent cardiac evaluation at a large cardiology clinic between 1997 and 2004.[31] AR and MR worsened in 15% and 25% of patients, respectively, were unchanged in 63% and 47%, and improved in 22% and 28% in this case series. Valvulopathy was reported well after the drug was discontinued in a few patients.[32,33]

Although many studies did not determine that dose of fenfluramine was a risk factor for development of drug-induced VHD, one abstract reported that a dose might play a role in the development of more severe valvulopathy.[34] In their analysis of a more severe subset of the original valvulopathy cases, there appeared to be an increased risk of developing more severe VHD in patients taking ≥60 mg/day as compared to <40 mg/day. The analyses were not available for review and the dataset was a subpopulation of a previously identified group, so firm conclusions regarding the role of dose in development of VHD cannot be drawn.

Pulmonary arterial hypertension (PAH) was associated with fenfluramine and dexfenfluramine prior to the U.S. FDA approval of these drugs[35]. PAH is characterized by restricted flow through the pulmonary arterial circulation, resulting in increased pulmonary vascular resistance and, ultimately, right heart failure.[36] This is a rare disease with a prevalence of 15/1,000,000. The prognosis of PAH is poor, with an approximately 15% mortality within 1 year on modern therapy.[37] In 1996, an epidemiological case-control study calculated that the use of appetite suppressants (primarily fenfluramine and dexfenfluramine) was associated with an increased risk of PAH (23-fold increase when used for more than 3 months).[35] As in the valvulopathy studies, the age of the patients (mean 44.7±12.3 years) was much greater than the proposed study population.

Diagnosis of PAH is more difficult than that of cardiac valvulopathy, as right heart catheterization is generally required for definitive PAH diagnosis. However, echocardiography has been used to screen for PAH by estimating pulmonary artery systolic pressure (PASP), as well as evaluating right heart hemodynamics. A major issue with the use of echocardiography to estimate PASP is lack of correlation with true PASP, when measured by right heart

[31] Dahl CF, et al. Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. BMC Medicine 2008, 6:34
[32] Greffe G, et al: Valvular heart disease associated with fenfluramine detected 7 years after discontinuation of treatment. Ann Thorac Surg 2007, 83:1541-1543.
[33] Prasad A, et al: Cardiac allograft valvulopathy: a case of donor-anorexigen-induced valvular disease. Ann Thorac Surg 1999, 68:1840-1841.
[34] Li R, Serdula MK, Williamson DF, et al. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. Int J Obes Relat Metab Disord. 1999;9(23):926-928.
[35] Abenhaim L, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. NEJM. 1996 Aug 29;335 (9):609-16.
[36] McLaughlin VV, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. Circulation. 2009 Apr 28;119(16): 2250-94.
[37] Thenappan T, et al. A USA-based registry for pulmonary arterial hypertension: 1982–2006. Eur Respir J. 2007;30:1103–10.

catheterization (underestimation more frequent than overestimation).[38] Additionally, at the time that the Applicant had submitted their original IND, there were no agreed-upon echocardiographic methods to diagnose PAH. For example, echocardiographic cutoffs of PASP >50 mmHg as "likely" and PASP 37-50 mmHg as "possible" pulmonary hypertension have been proposed by the European Task Force, but these are arbitrary, in the authors' opinion.[39] This initially raised concerns about use of echocardiography as screening for PAH in the IND study, especially because the Sponsor had not specified the normal ranges to be used.

The underlying mechanism by which fenfluramine causes the VHD or PAH is not entirely clear. It is well accepted that fenfluramine increases extracellular levels of serotonin in nervous tissue by a mechanism involving serotonin transporter proteins (SERT). Because of the observed similarity of the valvar abnormalities to that seen in carcinoid heart disease, and because fenfluramine and norfenfluramine (fenfluramine's active metabolite) are agonists at various 5-HT receptors, investigators initially surmised that serotonergic mechanisms were involved in the pathogenesis of fenfluramine-associated VHD. However, the current hypothesis is that fenfluramine-associated VHD is due to activation of $5\text{-}HT_{2B}$ receptors by norfenfluramine.[40] The underlying mechanism for fenfluramine-induced PAH remains unclear, although there are some nonclinical data suggesting that SERT overexpression may play a role.[41]

As noted above, there have been some published studies of fenfluramine use in patients with Dravet syndrome and pediatric patients with other neurological disorders. In brief, there are 46 studies of fenfluramine used (off-label) in children, primarily with autism or ADHD. Of these studies, 34 were controlled studies, which included a total of 502 children and adolescents. Age ranges vary for each study but were overall 2.5-30 years. Fenfluramine was dosed by mg/kg in most studies, ranging from 0.6 to 3.6 mg/kg/day with 1.5 mg/kg being the most common dose. The duration of patient exposure ranged from 1 month to 1 year; most were 3-4 months, and 7 of the studies were 9-12 months in duration. Adverse event collection and reporting were poorly-defined in most studies. Weight loss, sedation, irritability, and GI symptoms were the most commonly reported AEs. Three patients in these studies developed "grand mal" seizures in a setting of no previous seizures. No cardiac AEs or valvulopathy were reported in any of the studies, but it is unclear if the studies specifically assessed for valvulopathy with serial echocardiography. Efficacy was not conclusively demonstrated in any of the studies.

[38] Milan A, et al. Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. J Am Soc Echocardiogr 2010; 23: 225-39.
[39] Galie N, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society for Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30 (20): 2493-2537.
[40] Roth BL. Drugs and valvular heart disease. N Engl J Med 2007; 356:6-9
[41] Dempsie Y, Morecroft I, Welsh D, et al. Converging evidence in support of the serotonin hypothesis of dexfenfluramine-induced pulmonary hypertension with novel transgenic mice. Circulation 2008 117(22):2928-37

There are published data on a cohort of patients from Belgium with Dravet syndrome (DS) who have been treated with fenfluramine. The original published cohort[42] includes 12 patients who fulfilled the criteria for DS, 5 of whom were originally treated with fenfluramine for "self-induced" seizures and were diagnosed with DS after treatment began. Seven patients were enrolled prospectively with the diagnosis of DS. What is unclear from the article is if there were any patients who had been included in the program but were not included in the analysis.

The patients in the published cohort ranged in age from 3-35 years at publication (mean 19 years). At time that the drug was started, the mean age was 8 years (range 9 months to 16 years). At the time of publication, mean follow-up after fenfluramine was initiated was 11 years 4 months (range 1-22 years). All patients had drug-resistant epilepsy with multiple seizure types. Fenfluramine was administered to the patients most commonly as 5 or 10 mg BID, with a mean dose of 0.34 mg/kg/day (range 0.12-0.90 mg/kg/day). All patients were on other AEDs, 9 of whom were taking 3 concomitant AEDs. Six patients were treated with topiramate and benzodiazepines (clobazam, lorazepam, or ethyl loflazepate), 2 patients with lamotrigine, and 1 with levetiracetam and ethosuximide.

Fenfluramine was discontinued in 2 patients, 1 due to lack of efficacy and the other due to drug supply issues and persistent seizure-freedom off fenfluramine. Of the 10 patients still taking fenfluramine, 7 were seizure free at their last visit, 1 had ~75% reduction in seizure frequency (from 1/week to 1/month), and 2 had no reduction in seizure frequency (but they remained on the drug).

With respect to cardiac monitoring, it is unclear if there was regular cardiac monitoring early in the trial, but ultrasounds were performed yearly in the last three reported years of the study. PAH was not reported, but it is not clear if it was assessed. In two patients, a slight thickening of one or two heart valves was detected. In both patients (Patients (b) (6) and (b) (6)), these findings had remained stable for the prior year and were not considered clinically significant by the cardiologist. The patients remained on fenfluramine. Weight loss was reported in 2 patients, although the drug was not discontinued.

A second report of this cohort (the 10 remaining on fenfluramine plus 2 new patients) was published in 2015, describing only the prospective evaluation period.[43] All patients were treated with valproate, 6 of 12 were treated with topiramate, and 2 of 12 were treated with stiripentol. Seven patients received 10 mg/day, one received 15 mg/day, and four received 20 mg/day. Seizure control persisted: Of these 12 patients, 8 were seizure-free for at least two years. An increase in seizures was seen in one patient. Six patients had transient cardiac valve thickening which was seen on one echocardiogram but not on subsequent ones. One patient had valve thickening in the first 4 years but not on the last echocardiogram. None of these

[42] Ceulemans B, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia 2012; 53: 1131-1139.
[43] Ceulemans B. et al. Five-year follow-up of Fenfluramine as add-on treatment in Dravet syndrome. The European Paediatric Neurology Series, 2015 May 27-30. Vienna, Austria.

cardiac findings were associated with clinical symptoms. Anorexia occurred in 5 patients but was not "persistent." Fenfluramine was not discontinued in any patient due to AEs.

The original IND (125797) was initially placed on Clinical Hold because normative ranges for echocardiograms had not been included in the submission. As eligibility for enrollment was based on the lack of VHD and PAH both clinically and via echocardiogram, establishment of normative values was necessary prior to commencing the study to assure safety of patients participating in the study. A second reason for the Clinical Hold was that there was no provision for follow-up echocardiography after FEN was discontinued. Because VHD had been observed in patients even months after discontinuation of the drug, a follow-up echocardiogram was considered essential.

In their response to the Clinical Hold, Zogenix provided normative values and threshold criteria generated by their International Pediatric Cardiology Advisory Board. They proposed that these values be used to determine enrollment into the studies and continued participation if abnormalities on ECHO should occur.
Clinically meaningful ECHO findings were defined for pediatric patients in the protocol as follows:

1. *Definition of Clinically Meaningful Cardiac Valvulopathy if any one of the following ECHO findings are present (criteria apply to entire study age range):*
    a. *≥ mild valve regurgitation (aortic, mitral, tricuspid, or pulmonary)*
    b. *Mean Mitral valve gradient ≥ 4 mm Hg*
    c. *Mean Aortic valve gradient ≥ 15 mm Hg*
    d. *Mean Tricuspid valve gradient > 4 mm Hg*
    e. *Mean Pulmonary valve gradient > 21 mm Hg*
2. *Pulmonary Hypertension is suspected if the following ECHO findings are present (criteria apply to entire study age range):*
    a. *TR Jet velocity > 2.8 msec with or without the following findings OR*
    b. *one of the following findings in the absence of being able to measure TR Jet velocity:*
        i. *Change in right ventricle/left ventricle basal diameter ratio > 1.0*
        ii. *Right ventricular acceleration time < 100 msec*
        iii. *Dilatation of the inferior caval vein (diameter>21 mm and <50% inspiratory decrease) and/or right atrium*
        iv. *Change in the geometry of the interventricular septum in systole (flattening) with LV eccentricity index > 1.1 in systole and/or in diastole*
        v. *Early diastolic pulmonary regurgitation velocity > 2.2 m/sec*
        vi. *TAPSE below 18 mm or below Z-score – 2*

As part of their NDA, the Applicant submitted an Integrated Summary of Cardiovascular Safety (ISS-CV), the purpose of which was to characterize the cardiovascular safety in the Fintepla development program. The primary focus of the ISS-CV was the ECHO in assessment of mitral and aortic valves (particularly for regurgitation) and other analyses included measurements of pulmonary artery systolic pressure (PASP), assessment of tricuspid and pulmonic valves. For a detailed review of the ISS-CV, please see Dr. Shetarra Walker's review dated 18 DEC 2019.

As noted in Dr. Walker's review, the primary ECHO assessments specified in the study protocol included the following:

- *Number (%) of subjects with trace or greater regurgitation in mitral or aortic valves at each visit and overall in ISS-DB, LTS-DB (mitral valve only), and LTS populations*
- *Number (%) of subjects who developed VHD at any time during the program (ISS-DB and LTS populations). The FDA criteria for VHD in the mitral valve is moderate or worse regurgitation and for aortic valve is mild or worse regurgitation*
- *Number (%) of subjects with pulmonary artery systolic pressure (PASP) over 35 mmHg (ISS-DB and LTS Populations). Protocols defined a threshold for PAH as any PASP greater than 35 mmHg. The program employed "usual clinical practice" that any abnormal PASP findings were confirmed by repeat ECHO. If elevated PASP was not confirmed on repeat ECHO, then a subject was not considered to have PAH. All observed PASP values were presented…*

Secondary ECHO Analyses included:

- *Number (%) of subjects with trace or greater regurgitation in tricuspid and pulmonic valves at each visit and overall*
- *Number of subjects with absent or trace regurgitation at baseline who exhibited mild or greater regurgitation at end of study (ISS-DB and LTS populations)*
- *Summary of findings on valve structure and morphology*
- *Exploratory analyses on mitral valve changes -- due to the low incidence of regurgitation observed on the aortic valve, similar analyses are not included*
- *Heat maps for all valve scores to visualize longitudinal changes, if any, in regurgitation measures in individual subjects over time*
- *Trace or greater mitral regurgitation stratified by mean daily dose: > 0.48 mg/kg/day versus < 0.48 mg (0.48 mg/kg/day was the mean daily dose in the long-term, open-label study for all subjects)*
- *Trace or greater mitral regurgitation stratified by days of exposure: <90, 90-180, 181-270, or >271 days*
- *Mean change from baseline in PASP (mmHg) to end of study (ISS-DB and LTS Populations)*
- *Mean maximum change from baseline in PASP (mmHg) to end of study (ISS-DB and LTS populations)*
- *Number (%) of subjects with an increase in PASP from baseline ≥ 5, 10, and 15 mmHg (ISS-DB and LTS populations)*
- *Number (%) of subjects with normal baseline PASP with a PASP > 35 mmHg at Visit 12 (ISS-DB Population)*
- *Number (%) of subjects with any PASP findings > 35 mmHg post-baseline (ISS-DB and LTS Populations)*

Echocardiograms were performed at regular intervals during the controlled and uncontrolled studies, as follows:

- Study 1: screening, weeks 6 and 14, and 3 months after final dose

- Study 1504-C2: screening, weeks 6 and 12, and 3 months after final dose
- Study 1504-C1: screening, weeks 6, 12, and 26, and 3 months after final dose
- Study 1503: screening, months 1, 3, 6, 9, 12, 15, 18, 21, and 3 months after final dose

CV events were considered adverse events of special interest (AESIs). Initially, all aortic or mitral regurgitation events, regardless of severity or associated symptoms, were recorded as AESIs. However, due to the large number of trivial or trace aortic or mitral regurgitation observations (physiological findings), the Applicant amended study protocols to exclude trivial or trace regurgitation as an AESI.

The ISS-CV included echocardiogram data from a total of 232 patients enrolled in Studies 1, 1504-C1, 1504-C2, and 1503 by the cutoff date of 13 MAR 2018. An updated ISS-CV was included with the 120-Day Safety Update and included ECHO data from 330 patients (cutoff date of 14 OCT 2019). In Study 1503, 24/232 (10.3%) and 31/232 patients (13.4%) were exposed to >0.6 to 0.8mg/kg/day for at least 6 months and at least one year, respectively. In addition, 39/232 (16.8%) and 20/232 (6.3%) patients were exposed to 0.4 to 0.6 mg/kg/day for at least 6 months and at least one year, respectively. The majority of the patients who were taking 0.4-0.6 mg/kg/day were on concomitant STP, so the maximum dose allowed was 0.4 mg/kg/day.

No patient exhibited ECHO findings consistent with FDA-defined valvulopathy during Studies 1, 1504-C1, 1504-C2, and 1503 (Table 52). Overall, the proportion of trace or greater mitral regurgitation during double-blind treatment is larger in the pooled DB FEN treatment group 26/122 (21.3%) than in the placebo group, 8/84 (9.5%). Differences between groups was driven by trace regurgitation, which in the absence of structural valve abnormalities, is not considered pathologic.

As discussed elsewhere in this review, mild MR was identified in one patient during the controlled clinical trials. Mild MR had been present in this patient's initial screening ECHO but was not identified at a subsequent rescreening ECHO, which allowed the patient to be inappropriately enrolled into the study. One patient (# (b) (6)) had one transthoracic ECHO with a reading that met the FDA case definition for drug-associated valvulopathy (mild aortic regurgitation). However, the visualized jet reported by the readers was "abnormal", necessitating a diagnostic transesophageal echocardiogram (TEE) that revealed absent aortic regurgitation and normal aortic valve.

Table 52: Incidence of Mitral and Aortic Regurgitation during Controlled and Uncontrolled Studies

	Double-Blind Controlled Data					OLE Study
	Pooled Placebo N=84 n (%)	FEN 0.2 mg N=39 n (%)	FEN 0.8 mg N=40 n (%)	FEN 0.5 mg* N=43 n (%)	Pooled DB FEN N=122 n (%)	Variable doses N=232 n (%)
FDA-defined valvulopathy	0	0	0	0		0
Trace MR	8 (9.5%)	7 (17.9%)	9 (22.5%)	9 (20.9%)	25 (20.5%)	53 (22.8%)
Mild MR	0	0	0	1 (2.3%)	1 (0.1%)	0
Trace or greater AR	0	0	3 (7.5%)	0		1 (0.4%)

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ISS-CV, Table 10

Overall, there was no consistent relationship between duration of treatment and prevalence of trace or greater MR. The incidence of trace MR was similar across timepoints, ranging from 19.3% to 29.5%. The lowest incidence of 19.5% was observed in subjects exposed to study drug the longest, at least 361 days.

Zogenix performed a search of free-text comments in the ECHO reports to determine if any structural changes to any of the valves had been identified. One report included a comment describing possible annulus thickening of the tricuspid valve observed by one central ECHO reader but not the other at the 3-month ECHO in Study 1503. Both ECHO reviewers noted that images of the tricuspid valve were suboptimal. Two subsequent ECHO reports for this subject did not contain mention of tricuspid valve annulus thickening.

Pulmonary arterial systolic pressure was estimated via ECHO only from patients with measurable TR jets. In the controlled study population, 106/206 patients (51.5%) were evaluated, 46/84 (54.8%) in the placebo group and 60/122 (49.2%) in the pooled DB FEN group. In the LTS-DB population, 125/158 (79.1%) patients were evaluable for PAH, and 109/232 (47.0%) were analyzed for mean change in estimated PASP from baseline.

No cases of PAH have been identified in any patient through the cutoff date for the 120 Day Safety Update (14 OCT 2019). As per Dr. Walker's review, "*in the LTS-DB population, 2/125 evaluable subjects (1.6%) had an estimated PASP of > 35 mmHg, each at one reading. One subject, Subject* (b) (6)*, had an estimated PASP of ~40 mmHg on Study Day 365. Repeat echo performed 2 weeks later showed an estimated PASP ~19 mmHg. Follow up ECHOs obtained on Study Day 455 were read out as 'normal pressure' but no PASP estimate provided and on Study Day 545 estimated PASP was ~24 mmHg. The other subject, Subject* (b) (6)*, had an estimated PASP of ~36 mmHg on Study Day 180. Follow up ECHOs were performed on Study Day 270, which 'was not available,' Study Day 365 with estimated PASP of ~ 26 mmHg, and Day 455 with estimated PASP ~29 mmHg. Because all follow up ECHOs during the OLE for these subjects had*

normal PASP estimates, core lab and IPCAB cardiologists determined that neither subject had PAH.

Of those subjects who had PASP estimates, there was no obvious dose-dependent increase from baseline in estimated PASP compared to placebo. Zogenix assessed for relative increases in estimated PASP from baseline of at least 5 mmHg, 10 mmHg, or 15 mmHg. Most patients had a change in estimated PASP from baseline of less than 10 mmHg. In the ISS-DB population.

Cardiovascular adverse events were recorded and analyzed (Table 53). The majority of CV TEAEs were related to abnormal echocardiograms, which were more frequently reported in patients in the FEN groups (20/122, 16.4%) than in the placebo group (5/84, 6%). A total of 66 patients (19.9%) in the OLE study reported a TEAE of abnormal ECHO. None of the CV TEAEs were considered indicative of either VHD or PAH.

Table 53: Cardiac TEAEs, Controlled and Uncontrolled Populations

	Placebo N=84		FEN 0.2 mg N=39		FEN 0.8 mg N=40		FEN 0.5 mg** N=43		Pooled DB FEN N=122		Uncontrolled FEN N=331	
	n	%	n	%	n	%	n	%	n	%	n	%
Blood pressure increased	4	4.8%	5	12.8%	3	7.5%	0		8	6.6%	23	6.9%
Bradycardia	0		1	2.6%	0		1	2.3%	2	1.6%	2	0.6%
Echocardiogram abnormal*	5	6%	7	17.9%	9	22.5%	4	9.3%	20	16.4%	66	19.9%
Tachycardia	3	3.6%	2	5.1%	1	2.5%	0		3	2.5%	14	4.2%
Atrioventricular block	0		0		0		0		0		1	0.3%
Blood pressure decreased	0		0		0		0		0		1	0.3%
Pericardial effusion	0		0		0		0		0		1	0.3%
Ventricular extrasystole	0		0		0		0		0		1	0.3%

*Abnormal echocardiogram TEAE from transition period included in the controlled study population, as these were based on ECHO results from Visit 12 (last visit of maintenance period). Other TEAEs from transition period are included in the uncontrolled population
**0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADAE (ISS and 120-Day), via JMP

Reviewer's Comments: The Applicant conducted a prospective monitoring program for echocardiographic evidence of valvular heart disease and pulmonary arterial hypertension in the pediatric patients in their fenfluramine development program. This program included interval ECHO monitoring during the controlled and uncontrolled studies and a follow-up ECHO performed 3 months after the final dose of the investigational product. There were no findings of VHD or PAH in the development program as of the cutoff date for the 120-day safety update (14 OCT 2019).

Longer duration of treatment appeared to be a risk factor for development of fenfluramine-associated VHD and/or PAH, when fenfluramine and dexfenfluramine were used to treat obesity. The impact of dose of these drugs on development of VHD or PAH was not as clear when they were used as anorectic agents, although at least one study did

find a correlation. The overall absolute doses administered in the Fintepla development program (0.2-0.8 mg/kg/day, maximum 30 mg/day) are lower than those for which fenfluramine was approved as an anorectic agent (60-120 mg daily). However, the comparability of dose exposures of non-obese pediatric patients in the Fintepla development program to that of obese adults taking fenfluramine as an anorectic agent is unclear. It is quite possible that a non-obese child on a dose of 0.8 mg/kg/day or 30 mg/day might have similar dose-exposure to that of an obese adult taking 60 mg/day.

Although neither VHD nor PAH have been observed to date in the Fintepla development program, both of these disorders have been associated with the active ingredient in Fintepla and thus patients with DS who are prescribed Fintepla are at risk of developing fenfluramine-associated VHD or PAH. Many of the documented cases of fenfluramine-associated VHD or PAH were asymptomatic and identified via ECHO; therefore, monitoring for clinical symptoms is not sufficient to mitigate risk. Additionally, symptomatic cases may be more severe and more likely to require surgical intervention and/or lifelong medical treatment. Development of VHD or PAH, however, may be identified by regular monitoring via echocardiograms. An ECHO must be performed prior to starting the drug to determine if there is underlying cardiac disease and valvular function. ECHOs must be performed at regular intervals (every 6 months) to monitor for development of findings consistent with either VHD or PAH, regardless of the presence of symptoms. If findings consistent with either VHD or PAH are present on an ECHO, the treating clinician should assess benefit vs. risk, if they do not opt to discontinue the drug. Because VHD was reported in a few patients several months after discontinuation of fenfluramine, an ECHO will also be necessary 3 months after the final dose. Because ECHO monitoring is necessary for identifying VHD or PAH, a REMS with ETASU will be necessary, as is a box warning.

Lastly, the absence of findings of VHD or PAH in Fintepla development program does not mean that the risk in the refractory epilepsy population is lower than or different from the risks in the obese adult population who used fenfluramine and dexfenfluramine as anorectic agents. A PMR study and enhanced pharmacovigilance (PV) are both necessary to provide further information on the development of VHD and/or PAH in this population.

The PMR study should be designed to detect the signal of VHD or PAH. Additionally, it is possible that fenfluramine-associated valvulopathy might present differently in a pediatric non-obese population. As noted above, several patients in the long-term Belgian study developed "thickening" of the cardiac valve but not the FDA-defined VHD. Lastly, other factors may impact the risk of developing VHD or PAH in this population: demographics, concomitant drugs, underlying illnesses. These could all be captured in a PMR study.

Enhanced pharmacovigilance will provide closer postmarketing surveillance for cases of VHD and PAH in patients taking fenfluramine. The enhanced PV should include the following:

- **Submission of individual reports as 15-day expedited reports to the NDA and directly to DN2.**
- **Comprehensive summaries and analyses of these events quarterly as part of the required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].**
- **An assessment of causality for each case, with documentation of risk factors and results of all assessments that support the diagnosis (e.g., echocardiogram reports, pulmonary hemodynamic parameters) or the causality, along with information about dose and dose titration, duration of Fintepla therapy, time of event in relation to duration of therapy, associated signs and symptoms, concomitant therapies, treatment given for the event, and outcome of each event.**

8.5.2. Effects on Appetite and Weight

As noted in Section 8.4.5, TEAEs for decreased weight and decreased appetite were commonly reported AEs overall and reported more frequently in all of the FEN dose groups than in the combined placebo group (Table 54). Decreased appetite and decreased weight were frequently reported during the OLE study, as well. There was a general lack of correlation between decreased appetite and weight loss TEAEs. Patients who reported decreased appetite did not necessarily report weight loss, and vice versa. Several factors may lead to the lack of correlation between decreased appetite and weight loss, such as concomitant drugs that cause weight gain (valproic acid) or weight loss (topiramate), delay between decreased appetite and development of weight loss, special diets (e.g., ketogenic diet), underlying feeding difficulties in patients with DS, or use of a feeding tube to supplement oral intake. Lastly, some caregivers can overcome loss of appetite with specific foods.

A greater number of patients had significant weight loss than significant weight gain at the end of the controlled trials. Measured weight loss was noted more frequently in patients in the FEN groups than in the placebo groups in the controlled studies. At the end of the double-blind period, 2 (2.4%), 5 (12.8%), 8 (18.6%), and 10 (26.3%) patients had lost ≥7% of their baseline body weight while 13 (15.7%), 1 (2.6%), 2 (4.7%), and 0 (0%) had gained ≥7% of their baseline body weight in the placebo, FEN 0.2 mg/kg/day, 0.5 mg/kg/day, and 0.8 mg/kg/day groups, respectively (Table 55). As noted by the Applicant, more patients gained weight than lost after a year of fenfluramine treatment (Figure 5), consistent with long term trends generally seen in pediatric trials.

Reviewer's Comments: Weight loss and decreased appetite were reported more frequently in the FEN groups than in the combined placebo group, not unexpectedly, given that fenfluramine was originally approved as an anorectic agent. In fact, the most frequently-reported TEAE in the combined controlled FEN group was decreased appetite (37%) which was reported in only 8% of patients in the combined placebo group. Weight loss was also reported more frequently in the FEN group (8%), as compared to the placebo group (1%). Given that fenfluramine was previously approved as an anorectic drug, the

high incidence of decreased appetite, particularly in the FEN groups, is unsurprising. One patient in the 0.8 mg/kg/day group developed SAEs of decreased appetite and weight loss, leading to withdrawal from the study.

Decreased appetite was most frequently seen in patients in the 0.5 mg group (49%), as compared to 0.8 mg (37%), 0.2 mg (23%), and placebo (8%). Patients in the 0.5 mg group were taking concomitant STP, as were 5 of the 7 patients in the combined placebo group who experienced decreased appetite. The PI for STP carries a warning for decreased appetite and weight loss, which may have been a factor in the higher incidence of decreased appetite in the patients who received a combination of STP and FEN in Study 1504-C2.

Patients' weights and BMIs were recorded at each visit. There was an apparent dose response with respect to weight loss, during the controlled clinical trials, with the greatest incidence of patients with at least 7% or 10% weight loss occurring in the FEN 0.8 mg/kg/day dose group (26% and 11%, respectively) as compared to the other dose groups and placebo (see Table 55). This weight loss decreased over time, and by the time patients were on fenfluramine for 3 months in the OLE study, the incidence of patients overall with at least 7% or 10% weight gain was similar to incidence of patients with at least 7% or 10% weight loss.

TEAEs of weight loss and decreased appetite occurred much more frequently in patients taking FEN than placebo during the controlled studies. Additionally, significant weight loss (≥7% and ≥10% decrease from baseline weight) was observed more frequently in patients taking FEN than in patients in the placebo group during the controlled studies, although the continued weight loss appeared to taper off during the OLE study. While weight loss may be mitigated by concomitant drugs that cause weight gain and use of tube feeding, if available, patients with Dravet syndrome already are known to have underlying GI and feeding issues, which may lead to greater impact of weight loss. For these reasons, a warning for decreased appetite and weight decrease is necessary for safe use of fenfluramine, particularly in the DS population. Patients taking fenfluramine should be weighed at frequent intervals. Mitigation for decreased appetite and weight loss may be dose reduction or, if severe, discontinuation of the drug may be necessary.

Lastly, patients taking concomitant STP and FEN had the greatest incidence of decreased appetite, although this did not correlate with the highest incidence of weight loss. STP is one of only two other drugs specifically approved for treatment of seizures associated with DS, and it is highly likely that FEN will be administered concurrently with STP in these patients. Because of the likelihood of concomitant use of STP and FEN and the much greater incidence of decreased appetite in patients taking STP and FEN in Study 1504-C2 (48%), a warning about concomitant use of STP with FEN should be included in the proposed warning for decreased appetite and weight loss.

Table 54: Weight and Appetite TEAEs, Controlled Safety Population

	Placebo (N=84)	FEN 0.2 mg (N=39)	FEN 0.8 mg (N=40)	FEN 0.5 mg* (N=43)	Pooled DB FEN (N = 122)	Pooled Uncontrolled FEN (N=331)
Decreased appetite	7 (8.3%)	9 (23.1%)	15 (37.5%)	21 (48.8%)	45 (36.9%)	81 (24.5%)
Weight decreased	1 (1.2%)	5 (12.8%)	2 (5%)	3 (7%)	10 (8.2%)	27 (8.2%)

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ADAE (ISS) in JMP

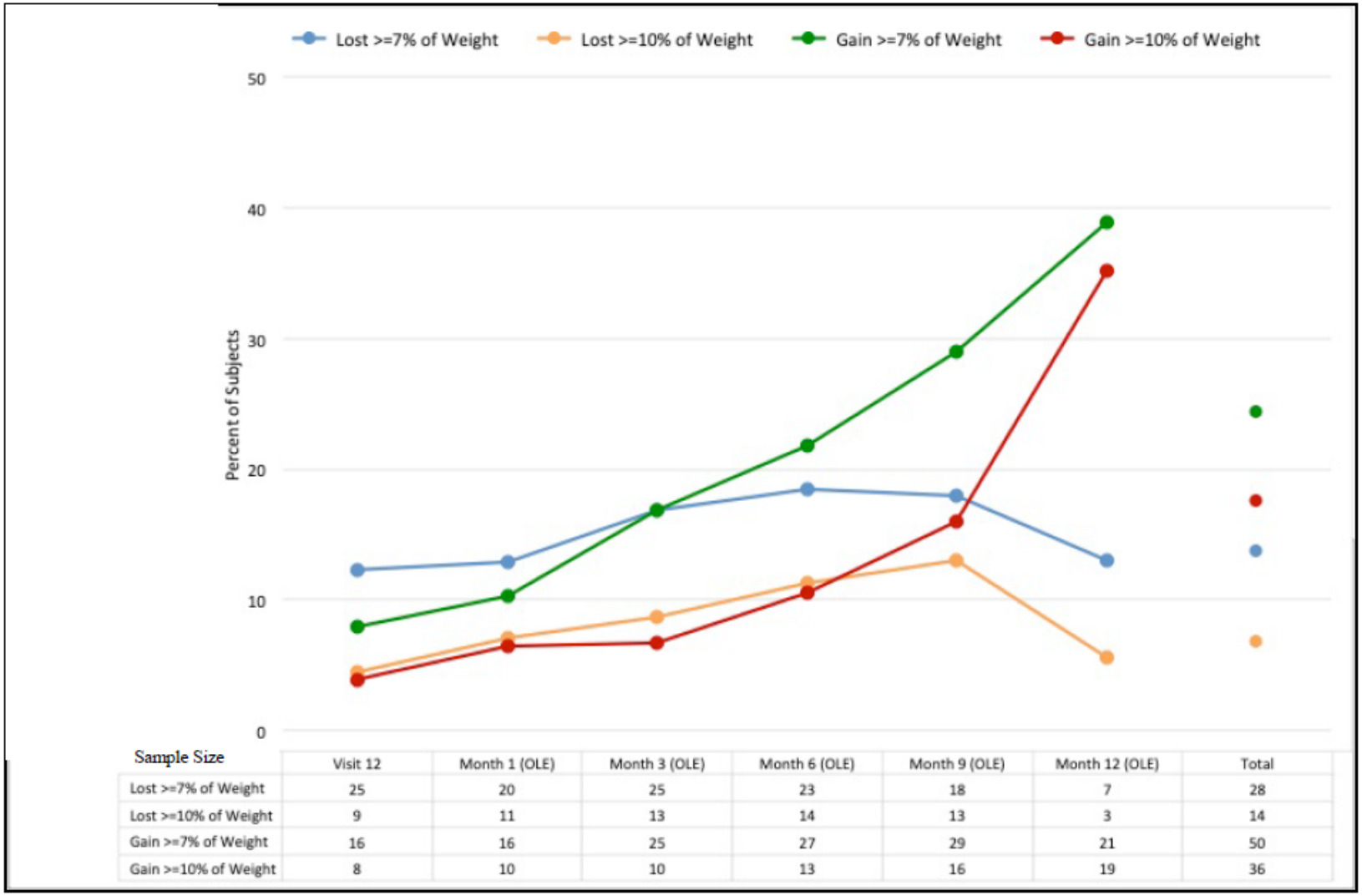
Table 55: Summary of Body Weight Gain or Loss (Categories), During the Double-blind Through Open-label Study Periods, Controlled/Uncontrolled Populations

	Placebo (N=84)	FEN 0.2 mg (N=39)	FEN 0.8 mg (N=40)	FEN 0.5 mg* (N=43)	All patients (N=206)
Visit 12, n	**83**	**39**	**38**	**43**	**203**
Lost ≥7% of Weight	2 (2.4%)	5 (12.8%)	10 (26.3%)	8 (18.6%)	25 (12.3%)
Lost ≥10% of Weight	0 (0.0%)	3 (7.7%)	4 (10.5%)	2 (4.7%)	9 (4.4%)
Gain ≥7% of Weight	13 (15.7%)	1 (2.6%)	0 (0.0%)	2 (4.7%)	16 (7.9%)
Gain ≥10% of Weight	6 (7.2%)	1 (2.6%)	0 (0.0%)	1 (2.3%)	8 (3.9%)
Month 1 (OLE), n	**63**	**38**	**34**	**20**	**155**
Lost ≥7% of Weight	3 (4.8%)	7 (18.4%)	6 (17.6%)	4 (20.0%)	20 (12.9%)
Lost ≥10% of Weight	1 (1.6%)	4 (10.5%)	4 (11.8%)	2 (10.0%)	11 (7.1%)
Gain ≥7% of Weight	9 (14.3%)	5 (13.2%)	2 (5.9%)	0 (0.0%)	16 (10.3%)
Gain ≥10% of Weight	7 (11.1%)	2 (5.3%)	1 (2.9%)	0 (0.0%)	10 (6.5%)
Month 3 (OLE), n	**58**	**38**	**35**	**18**	**149**
Lost ≥7% of Weight	6 (10.3%)	8 (21.1%)	8 (22.9%)	3 (16.7%)	25 (16.8%)
Lost ≥10% of Weight	1 (1.7%)	6 (15.8%)	5 (14.3%)	1 (5.6%)	13 (8.7%)
Gain ≥7% of Weight	12 (20.7%)	6 (15.8%)	4 (11.4%)	3 (16.7%)	25 (16.8%)
Gain ≥10% of Weight	6 (10.3%)	2 (5.3%)	2 (5.7%)	0 (0.0%)	10 (6.7%)
Month 6 (OLE), n	**45**	**37**	**34**	**8**	**124**
Lost ≥7% of Weight	2 (4.4%)	10 (27.0%)	9 (26.5%)	2 (25.0%)	23 (18.5%)
Lost ≥10% of Weight	1 (2.2%)	6 (16.2%)	6 (17.6%)	1 (12.5%)	14 (11.3%)
Gain ≥7% of Weight	14 (31.1%)	6 (16.2%)	6 (17.6%)	1 (12.5%)	27 (21.8%)
Gain ≥10% of Weight	8 (17.8%)	3 (8.1%)	1 (2.9%)	1 (12.5%)	13 (10.5%)
Month 9 (OLE), n	**35**	**32**	**31**	**2**	**100**
Lost ≥7% of Weight	1 (2.9%)	10 (31.3%)	6 (19.4%)	1 (50.0%)	18 (18.0%)
Lost ≥10% of Weight	1 (2.9%)	7 (21.9%)	4 (12.9%)	1 (50.0%)	13 (13.0%)
Gain ≥7% of Weight	10 (28.6%)	8 (25.0%)	11 (35.5%)	0 (0.0%)	29 (29.0%)
Gain ≥10% of Weight	6 (17.1%)	4 (12.5%)	6 (19.4%)	0 (0.0%)	16 (16.0%)
Month 12 (OLE), n	**18**	**19**	**17**	**0**	**54**
Lost ≥7% of Weight	0 (0.0%)	4 (21.1%)	3 (17.6%)	0 (0.0%)	7 (13.0%)
Lost ≥10% of Weight	0 (0.0%)	2 (10.5%)	1 (5.9%)	0 (0.0%)	3 (5.6%)
Gain ≥7% of Weight	7 (38.9%)	8 (42.1%)	6 (35.3%)	0 (0.0%)	21 (38.9%)
Gain ≥10% of Weight	6 (33.3%)	7 (36.8%)	6 (35.3%)	0 (0.0%)	19 (35.2%)

	Placebo (N=84)	FEN 0.2 mg (N=39)	FEN 0.8 mg (N=40)	FEN 0.5 mg* (N=43)	All patients (N=206)
Total, n	**83**	**39**	**40**	**43**	**205**
Lost ≥7% of Weight	3 (3.6%)	10 (25.6%)	8 (20.0%)	7 (16.3%)	28 (13.7%)
Lost ≥10% of Weight	1 (1.2%)	7 (17.9%)	4 (10.0%)	2 (4.7%)	14 (6.8%)
Gain ≥7% of Weight	22 (26.5%)	14 (35.9%)	11 (27.5%)	3 (7.0%)	50 (24.4%)
Gain ≥10% of Weight	14 (16.9%)	11 (28.2%)	9 (22.5%)	2 (4.7%)	36 (17.6%)

*0.5 mg/kg is not an intermediate dose. Patients in the 0.5 mg/kg/day group were also taking concomitant STP, which increases exposure of FEN
Source: ISS, Table 54, verified in JMP

Figure 5: Weight Change Over Time, Controlled and Uncontrolled Populations



Sample Size	Visit 12	Month 1 (OLE)	Month 3 (OLE)	Month 6 (OLE)	Month 9 (OLE)	Month 12 (OLE)	Total
Lost >=7% of Weight	25	20	25	23	18	7	28
Lost >=10% of Weight	9	11	13	14	13	3	14
Gain >=7% of Weight	16	16	25	27	29	21	50
Gain >=10% of Weight	8	10	10	13	16	19	36

Source: ISS, Figure 4, based on verified data

8.5.3. Central Nervous System TEAEs

As noted in Section 8.4.5, somnolence (including sedation and lethargy) and fatigue (including malaise and asthenia) were notably more frequently reported in patients taking FEN than in patients taking placebo, during the controlled studies. Fatigue was reported in 19% of patients in the pooled DB FEN group and in 5% of patients in the combined placebo group for an attributable risk difference of 14%. Somnolence was reported in 25% and 11% of patients in the pooled FEN and placebo groups, respectively, and also had an attributable risk difference of 14%. However, a dose response was not seen with either somnolence or fatigue. A total of 36 patients (11%) in the uncontrolled population reported somnolence, while 10% of patients reported fatigue. Three patients in the 0.8 mg group discontinued participation in the study due to a TEAE of somnolence. No patients discontinued due to somnolence or fatigue during the OLE study.

Abnormal behavior; drooling and hypersalivation; gait disturbance, ataxia, and balance disorder; insomnia and other sleep disorders; and tremor were also reported at higher frequencies in the FEN group than in the placebo group, and generally at notable frequencies in the OLE study. For these adverse events, the frequencies were similar at the 0.2, 0.5, and 0.8 mg/kg/day doses in the controlled trials. Given that the drug crosses the blood-brain barrier, and in light of the relatedness of some of the events, these are reasonably likely to be drug-related and should be included as adverse reactions in Section 6 of labeling.

8.5.4. Systemic Hypertension

As noted above, fenfluramine increases the extracellular levels of serotonin in nervous tissue, in part by increasing extrasynaptic serotonin levels through modulation of serotonin receptors (primarily 5-HT_{1A} receptors). However, the active metabolite of fenfluramine (norfenfluramine), has affinity for 5-HT_{2A} and 5-HT_{2B} receptors. A number of 5-HT receptor subtypes (primarily 5-HT_{1B} and 5-HT_{2A}) have been shown to mediate vasoconstriction of systemic arteries.[44] Norfenfluramine in particular, has been shown to cause contraction of smooth muscle and elevated blood pressures in rats.[45] Significant elevations in systemic blood pressure have been reported with other drugs which increase serotonin, particularly 5-HT_1 agonists. The triptan labels have a class warning for hypertension and hypertensive crisis, due to this adverse effect.

Hypertension, including hypertensive crisis, has been reported in the literature in patients taking fenfluramine.[46] In a small case series published in 1975, Mabande identifies 5 patients who developed significant elevations in systolic and/or diastolic blood pressures while taking fenfluramine. Four of the patients had pre-existing hypertension and were on concomitant anti-hypertensive drugs; one patient did not have a history of hypertension and was on no

[44] Kaufman AJ, Levy FO. 5-Hydroxytryptamine receptors in the human cardiovascular system. Pharm & Therap 111 (2006) 674–706
[45] Ni W, Li MW, Thakali K, et al. The Fenfluramine Metabolite (+)-Norfenfluramine Is Vasoactive. J Pharm Exp Therap, 2004 Vol. 309, No. 2; 845-852
[46] Mabadeje AF. Fenfluramine associated hypertension. West African J Pharm and Res, Dec 1975; Vol2 No 2;145-

concomitant drug for hypertension. A positive dechallenge was reported in all 5 cases, as the blood pressure returned to baseline once fenfluramine was discontinued (normotensive in 3, hypertensive in 2). One case reported a positive rechallenge. All of the patients had at least one blood pressure reading consistent with hypertensive crisis (systolic BP ≥180 or diastolic BP ≥110). No end organ damage or persistent effects were reported in any of these patients.

TEAEs of hypertension or increased blood pressure were seen more frequently in patients in the pooled FEN group (10/122, 8.2%) than in the placebo group (4/84, 4.8%). There was no clear dose effect of hypertension/increased blood pressure: 6/39 patients (15.4%) in the 0.2 mg group, 4/40 (10%) of patients in the 0.8 mg group and 0 patients in the 0.5 mg group. Small decreases were seen in systolic and diastolic blood pressure, and heart rate at Visit 12 in the ZX008 0.5 mg/kg/day treatment group which were not considered clinically significant There were no clinically significant changes in measured systolic or diastolic blood pressures, nor differences between treatment groups, in the controlled trials.

Reviewer's comment: There have been reports in published literature of hypertension, including hypertensive crisis, in patients taking fenfluramine, as well as literature describing the mechanism by which fenfluramine and its active metabolite, norfenfluramine, may cause elevated blood pressure. During the controlled clinical studies, there was a greater incidence of hypertension or elevated blood pressure in patients in the pooled FEN group (8.2%) compared to that in the pooled placebo group (4.8%), although there was no dose-effect. Because of the plausible mechanism, reports of hypertensive crisis (including one positive rechallenge) in published literature, and higher rates of hypertension in the pooled FEN group compared to placebo, this adverse effect should be included as a Warning in the PI.

8.6. Safety Analyses by Demographic Subgroups

TEAEs were examined by age subgroup (<6 years and ≥6 years) in the pooled dataset. Fifty-five (27%) of patients who received at least one dose of FEN in Studies 1 and 1504-C2 were 2 to <6 years of age and 151 (73%) were 7 to ≥6 years of age. Although the overall incidence of TEAEs was greater in the younger group (91%) than in the older group (85%), many of the common TEAEs, especially ones not related to infection, were more frequently reported in the ≥6 years age group (Table 56).

Table 56: Frequent TEAEs by Age Group (<6 and ≥6 years), Controlled Safety Population

	Placebo N=84				Pooled DB FEN N=122			
	<6 years		≥6 years		<6 years		≥6 years	
Dictionary-Derived Term	n	%	n	%	n	%	n	%
Decreased appetite	1	1.2%	6	7.1%	10	8.2%	35	28.7%
Diarrhea	3	3.6%	2	2.4%	13	10.7%	15	12.3%
Echocardiogram abnormal	1	1.2%	4	4.8%	3	2.5%	17	13.9%
Fatigue	0	0.0%	4	4.8%	7	5.7%	16	13.1%

Dictionary-Derived Term	Placebo N=84				Pooled DB FEN N=122			
	<6 years		≥6 years		<6 years		≥6 years	
	n	%	n	%	n	%	n	%
Seizure	6	7.1%	11	13.1%	4	3.3%	6	4.9%
Somnolence	1	1.2%	8	9.5%	8	6.6%	22	18.0%
Weight decreased	1	1.2%	0	0.0%	2	1.6%	8	6.6%

Source: ADAE ISS, JMP

8.7. Specific Safety Studies/Clinical Trials

Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients 7 years and older were administered the age-appropriate version of the C-SSRS if they were considered capable of completing the questionnaire by the investigator. The C-SSRS was assessed in Studies 1 and 1504-C2 at the screening visit (visit 1), at randomization (visit 3), titration period (at visit 6), maintenance period (at visits 8 and 10) and at EOS (visit 12). The proportion of patients who completed the C-SSRS ranged from 35% to 52.3%.

In Study 1, 14/40 (35.0%) of placebo patients, 18/39 (46.2%) of patients in the 0.2 mg group, and 20/40 (50.0%) of patients in the 0.8 mg group completed the questionnaire. No patients in any of the 3 treatment groups reported an instance of any C–SSRS parameter at any visit.

In Study 1504 Cohort 2, 23/44 (52.3%) patients in the placebo group and 20/43 (46.5%) patients in the 0.5 mg group completed the questionnaire during the T+M period. One patient (# (b) (6) (b) (6) in the 0.5 mg/kg/day group) was reported to be exhibiting self-injurious behavior without suicidal intent at baseline and at visits 6, 8, 10, and 12 (EOS visit). This behavior persisted in the OLE study (through Month 18 visit).

In Study 1503, 145/330 (43.9%) patients completed the C-SSRS at baseline (Visit 1 of OLE) and at various timepoints during the OLE period. One patient (# (b) (6)) reported suicidal ideation during (b) (4) which persisted into the OLE study.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable

8.8.2. Human Reproduction and Pregnancy

No studies were conducted with fenfluramine in pregnant women to assess risks. No pregnancies were reported during the development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

See Section 8.5.2 above.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported during the development program. No AEs consistent with withdrawal phenomena were reported during the taper/transition period of the controlled studies.

Overdoses of fenfluramine have been reported in published literature. Dr. Karen Long (Division of Pharmacovigilance) performed a FAERS search and identified 55 reports of fenfluramine overdose in published literature, 10 of which were fatal. The doses in these reports ranged from 200 mg to 2000 mg, all of which are significantly greater than the doses used in the Fintepla clinical trials and in the proposed labeling. Most occurred in pediatric patients. Seventeen of 21 cases in which age was reported were in patients < 17 years of age, and 8 of the 10 fatal cases were in children.

The most frequently reported adverse events in all cases of overdose included mydriasis, tachycardia, flushing, tremors/twitching/muscle spasms, agitation/restlessness/anxiety, increased muscle tone/rigor/opisthotonos, respiratory distress or failure, and seizure. The most frequently reported adverse events in the 10 fatal cases included seizure, coma, and cardiorespiratory arrest resulting in death.

The median time at which symptoms began after overdose was 1 hour (0.5-3.5 hours). Of the 16 cases which reported time to presentation, 9 presented to the hospital with adverse events within 1 hour of ingestion. As per Dr. Long's review, the *"median time to death after ingestion was 8.5 hours (range 2-240 hours), and 5 fatal cases reported death within 3.5 hours of ingestion."*

Reviewer's comment: There were no reports of fenfluramine overdose during the Fintepla clinical trials, however, there have been a number of reports of overdose of fenfluramine in published literature, 10 of which were fatal. The Applicant's proposed wording in the PI, is inconsistent with the severity of events in some of these case reports and does not address that there were fatalities. Because of the severity of some of the cases, the number of fatal cases, the high percentage of overdose in pediatric patients, and the short time to death in some cases, the Overdosage section of the PI has been revised to reflect this information.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Fenfluramine is not currently marketed.

8.9.2. Expectations on Safety in the Postmarket Setting

In general, I expect that the patterns of adverse reactions in the postmarket setting will be similar to those seen during the controlled and uncontrolled clinical studies. Given that

suicidality is higher in patients with epilepsy, there will eventually be suicides reported on the drug; however, these will likely be difficult to interpret.

The risk of fenfluramine-associated VHD and PAH is unknown at this time in the pediatric Dravet population. As discussed in Section 8.5.1, the impact of the lower absolute dose of Fintepla on this risk is, as yet, unknown. The lower dose may be offset by an eventual longer duration of treatment (overall dose). Additionally, the comparability of dose-exposures if 60-120 mg/day in obese adults to 0.2-0.8 mg/kg/day (maximum of 30 mg/day) in non-obese children or adolescents is unclear.

In order to be prescribed Fintepla, all patients will be subject to a REMS with ETASU. All patients must have a baseline ECHO prior to starting the drug and have ECHOs every 6 months in order to remain on it. As part of the REMS program, all patients will be enrolled in a registry to closely monitor their cardiac status.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Fenfluramine was originally approved by U.S. FDA in 1973 as an anorectic agent but was withdrawn in 1997 due to the association between fenfluramine and valvular heart disease and pulmonary arterial hypertension. To support the safety of fenfluramine in the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older, the Applicant has provided safety data primarily from two controlled clinical trials and one long-term safety study, as well as from a small PK study.

The total number of unique patients who were exposed to fenfluramine during the DS development program prior to the cutoff date for the 120-day safety update was 341. The Applicant performed safety analyses on Studies 1, 1504-C2, 1504-C1, and 1503 separately, as well as on pooled datasets. The primary FDA safety analyses were performed on the following pooled datasets:

- Controlled safety population: Studies 1 and 1504-C2, including TEAEs from the titration and maintenance periods only
- Uncontrolled safety population: Study 1504-C1, transition/taper periods from Studies 1 and 1504-C2, and 1503 (b) (4) through the cutoff date for the 120-Day Safety Update.

Four deaths were reported during the development program, all attributed to SUDEP. One death occurred during the blinded phase (b) (4), and the treatment allocation for that patient remains blinded. SUDEP is more commonly observed in patients with DS than in childhood epilepsy in general. It is not possible to attribute the deaths to fenfluramine.

The overall incidence of treatment-emergent SAEs was 10.7% in the controlled safety population with similar incidences in the pooled FEN group (9%) as compared to the placebo group (12%). The most-frequently reported SAEs in the pooled FEN group were status epilepticus (4, 3.3%) and somnolence (3, 2.5%). In the placebo patients, seizure (6, 7.1%) was the most frequently seen serious TEAE. Each remaining SAE was reported by only 1 or 2 patients. The types and frequencies of TEAEs reported in Studies 1 and 1504-C2 are similar to those seen in other trials of refractory epilepsy in pediatric patients.

A total of 13 patients (6.3%) discontinued FEN due to a TEAE in Studies 1 and 1504-C2. The incidences were similar between groups: 8 (6.6%) of pooled FEN patients and 5 (6.0%) of placebo patients. The most common causes of discontinuation due to TEAE in the FEN group were decreased appetite (n=2, 1.6%) and somnolence/lethargy (n=3, 2.7%), while seizures were the only reason for discontinuation due to TEAE in the placebo group. All but one patient who discontinued participation due to an adverse event did so during the maintenance period.

Certain adverse events of special interest were specifically evaluated. Cardiovascular TEAEs were of special interest due to the fenfluramine-associated VHD and PAH discussed above. The majority of CV TEAEs were related to abnormal echocardiograms, which were more frequently reported in patients in the FEN groups (20/122, 16.4%) than in the placebo group (5/84, 6%). A total of 66 patients (19.9%) in the OLE study reported a TEAE of abnormal ECHO. None of the CV TEAEs were considered indicative of either VHD or PAH. Additionally, no patient exhibited ECHO findings consistent with FDA-defined valvulopathy during Studies 1, 1504-C1, 1504-C2, and 1503.

Effects on weight and appetite were also specifically assessed. Decreased appetite and weight decrease were seen more frequently in the pooled FEN group (37% and 8%, respectively) than in the placebo group (8% and 1%, respectively). There was no clear dose response for these findings, with greater frequency of weight decreased in 0.2 mg group compared to the 0.5 and 0.8 mg group, and greatest frequency of decreased appetite in the 0.5 mg group. Decreased appetite is especially notable because of the overall frequency of the event and the high-risk difference (28.6%). There was an apparent dose response for measured weight loss during the controlled trials with 2.4%, 12.8%, 18.6% and 26.3% of patients in the placebo, 0.2 mg, 0.5 mg, and 0.8 mg groups respectively had lost at least 7% of their baseline weight by the final visit of the controlled studies. Weight loss did appear to slow down significantly during the OLE study, suggesting that this effect waned over time or could be mitigated by increased feeding, change in diet, or even supplemental tube feedings. There appeared to be a potentially synergistic effect of stiripentol and fenfluramine on appetite, as the incidence of decreased appetite in the 0.5 mg group (49%) was notably greater than that in the 0.2 mg (23%) and 0.8 mg (38%) groups. Five of the seven patients in the placebo group who experienced decreased appetite were on concomitant STP.

During the controlled trials, somnolence (including sedation and lethargy) and fatigue (including malaise and asthenia) were reported notably more frequently in patients taking FEN (25% and 19%, respectively) than in patients taking placebo (11% and 5%, respectively). However, a dose

response was not seen with either somnolence or fatigue. Three patients in the 0.8 mg group discontinued participation in the study due to a TEAE of somnolence.

Rash occurred in 7% of FEN patients and 4% of placebo patients, leading to discontinuation in only one patient (placebo). No patients reported a SAE related to rash.

Two patients were reported as exhibiting suicidality during the development program. One patient in the FEN 0.5 mg group in Study 1504-C2 was reported to be exhibiting self-injurious behavior without suicidal intent at baseline and all visits through OLE Month 18. One patient reported suicidal ideation during (b) (4) which persisted mildly into the OLE study. These particular findings do not raise clinical concerns.

Small decreases in the mean and median platelet counts from baseline were seen in all FEN groups compared to placebo, although the mean and median values remained within the normal reference ranges. There was no dose response seen during the controlled trials with change from baseline of platelet counts. Rare TEAEs for thrombocytopenia or decreased platelet counts were reported but no changes to drug dosing occurred as a result of these TEAEs or lab findings. There were no cases of drug-induced liver injury. No patient met Hy's law criteria. No patients discontinued treatment due to LFT abnormalities or liver dysfunction.

In summary, fenfluramine's most serious safety concern is the risk of developing valvular heart disease and/or pulmonary arterial hypertension. Although no cases of VHD or PAH have been reported to date in the Fintepla Dravet development program, fenfluramine-associated VHD and PAH remain known risks to patients and any patients who are administered the drug require cardiac follow-up with baseline and interval echocardiograms.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not deemed necessary for this submission

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been proposed, but the labeling has not been finalized at the time of this review.

The doses of fenfluramine in the PI differ from those used in the studies, because the Applicant implemented the USP Salt Policy.[47] The dose of 0.8 mg/kg/day (maximum 30 mg/day) used in

[47] https://www.fda.gov/media/87247/download#

Study 1 is roughly equivalent to the 0.7 mg/kg/day (maximum 26 mg/day) in the proposed PI. Similarly, the proposed dose of 0.4 mg/kg/day (maximum 17 mg/day) in patients on concomitant STP is roughly equivalent to the 0.5 mg/kg/day (maximum 20 mg/day) dose in Study 1504-C2. The 0.2 mg/kg dose in the label is the same as that used in the studies.

At the time this review was completed, my recommended warnings for the prescription drug labeling were as follows:

- Valvular Heart Disease and Pulmonary Arterial Hypertension (REMS and boxed warning): see Sections 8.5.1 and 11.
- Decreased Appetite and Decreased Weight: see Section 8.5.2
- Somnolence, Sedation, and Lethargy: see Section 8.5.3
- Increase in Blood Pressure: see Section 8.5.4
- Serotonin Syndrome: Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS). It is seen with medication use at therapeutic doses, DDIs, and overdosage. Serotonin syndrome is a clinical diagnosis, most commonly including mental status changes (anxiety, agitation, delirium, restlessness, disorientation), autonomic hyperactivity (diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, diarrhea), and neuromuscular abnormalities (tremor, rigidity, myoclonus, hyperreflexia, clonus, bilateral Babinski sign). Any serotoninergic drug is at risk of causing serotonin syndrome, although stimulation of the postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors has been implicated in serotonin syndrome. A warning for serotonin syndrome is included in the prescribing information for most, if not all, drugs with serotonergic activity. As fenfluramine increases extracellular serotonin activity, development of serotonin syndrome is an anticipated risk.
- Glaucoma: The Applicant proposed a warning for glaucoma in the prescribing information. (b) (4)

(b) (4)

[48] Yang MC and Lin KY. Drug-induced Acute Angle-closure Glaucoma: A Review. J Curr Glauc Prac, 2019; 13;3:104-109
[49] Wang H, Tseng P, Stubbs B, et al. The Risk of Glaucoma and Serotonergic Antidepressants: A Systematic Review and Meta-Analysis. J Affect Disord 2018 Dec 1;241:63-70
[50] Eke T, Carr S. Acute glaucoma, chronic glaucoma, and serotoninergic drugs. Br J Ophthal 1998;82:976–979
[51] Denis P, Charpentier D, et al. Bilateral Acute Angle-Closure Glaucoma After Dexfenfluramine Treatment. Ophthalmologica. 1995;209(4):223

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

Please see the Division of Risk Management's review for a complete discussion of the planned REMS with elements to assure safe use (ETASU) for Fintepla. This submission was presented to a meeting of the REMS Oversight Committee on January 9, 2020.

As discussed in Section 8.5.1, fenfluramine was associated with the development of VHD and PAH when it was previously used as an anorectic agent in adults with obesity. Although there were no findings on ECHOs consistent with VHD or PAH during the development for fenfluramine in patients with DS, the risk of developing either of these potentially serious and life-threatening disorders remains. Labeling is insufficient to mitigate the risk of VHD or PAH, especially as many cases, even a few that required management with drugs or surgery, were asymptomatic when the VHD or PAH was identified on ECHO prior to the drug being withdrawn from the market in the 1990's. However, regular monitoring via ECHO is likely to reduce the risk by early identification of VHD and/or PAH and allow for determination of benefit vs. risk if abnormal findings on ECHO are identified.

A REMS with ETASU is necessary for fenfluramine to be used safely to treat seizures in patients with DS because of the previously-identified fenfluramine-associated valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). The ETASU for this REMS will include the following elements: prescriber certification, pharmacy certification, safe use conditions, monitoring and a REMS registry. Specifically, prescribers must be educated on the risk of VHD and PAH associated with fenfluramine, the need to inform patients about these risks and how to recognize signs and symptoms of VHD and PAH, the requirement to submit the necessary documentation regarding baseline and interval echocardiograms to the REMS, and the requirement that all patients be enrolled in the REMS program to receive the drug. The REMS program will ensure that patients are taught to recognize and respond to symptoms and signs of VHD and PAH and that baseline and interval ECHO monitoring is required. Finally, the REMS will ensure that all patients are enrolled in a registry.

12. Postmarketing Requirements and Commitments

The following safety postmarketing requirements have been identified:

- A prospective observational registry study in epilepsy patients taking Fintepla using data from the REMS Registry and additional data beyond what is collected in the REMS Registry. The primary objectives are to characterize the risks of the development of

symptomatic or asymptomatic valvular heart disease (VHD) and/or pulmonary arterial hypertension (PAH). This includes recruiting an adequate number of patients to assess the incidence of VHD and PAH, to identify risk factors for VHD and PAH, and to evaluate the impact of duration, dose-exposure, and cumulative exposure on the development of VHD and PAH. Evaluation should include the assessment of echocardiographic data; patients in the study should be evaluated with echocardiograms at baseline and every six months for five years, or until the last echocardiogram following interruption of Fintepla treatment.
PMR dates (as of the time this review was finalized):
Draft Protocol Submission: 12/2020
Final Protocol Submission: 08/2021
Study Completion: 08/2031
Final Report Submission: 08/2032

- A single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to FINTEPLA (fenfluramine) during pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (b) (4) measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis (b) (4) (b) (4).
  PMR dates (as of the time this review was finalized):
  Draft Protocol Submission: 12/2020
  Final Protocol Submission: 08/2021
  Study Completion: 08/2032
  Final Report Submission: 08/2033

Postmarketing requirements recommended by other disciplines:

- Nonclinical:
  - A fertility and early embryonic development study of fenfluramine in rat.
  - An embryofetal development study of fenfluramine in rat.
  - An embryofetal development study of fenfluramine in rabbit.
  - A pre- and postnatal development study of fenfluramine in rat.
  - A (b) (4) carcinogenicity study of fenfluramine in mouse.
  - A 2-year carcinogenicity study of fenfluramine in rat.
- Clinical Pharmacology:
  A clinical pharmacokinetic trial to determine an appropriate dose of FINTEPLA (fenfluramine) to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

13. Appendices

13.1. References

See footnotes throughout document.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1 (1501, 1502) and 1504-C2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1: 54, 1504-C2: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Study Details

Echocardiographic Thresholds for DSMC Evaluation, Studies 1, 1504-C2, 1504-C1, and 1503
Thresholds that will bring subjects to review of the DSMC are as follows:

	VALVULOPATHY	***PULM HYPERTENSION***
Level (1) Continue Monitoring as per protocol	- *No pathologic aortic or mitral regurgitation** - *Mitral valve gradient (mean) < 4 mm Hg* - *Aortic valve gradient (mean) < 15 mm Hg* - *Tricuspid valve gradient (mean) < 4 mm Hg* - *Pulmonary valve gradient (mean) < 21 mm Hg*	*TR Jet Vel < 2.8 msec*

Using the Webb et al (2015) criteria[52], if patients exhibit "physiologic" regurgitation at baseline, they will be graded as "trace" regurgitation, have their echocardiograms reviewed by the Pediatric CV Ad Board for confirmation and, if they agree, be allowed into the study and monitored per the clinical protocol.

	VALVULOPATHY	***PULM HYPERTENSION***
Level (2) Secondary Adjudication by CV Ad board members with Recommendation to IDSMC weighing Risk/Benefit" to continue treatment*	- *≤ Mild aortic or mitral regurgitation* - *Mitral valve gradient (mean) ≥ 4 mm Hg without any clinical or ECHO signs of left heart failure* - *Aortic valve gradient (mean) ≥ 15 mm Hg without any clinical or ECHO signs of left heart failure* - *Tricuspid valve gradient (mean) ≥ 4 mm Hg without any clinical or ECHO signs of right heart failure* - *Pumonary* [sic] *valve gradient (mean) ≥ 21 mm Hg without any clinical or ECHO signs of right heart failure*	*TR Jet Vel of 2.9 to 3.4 msec*

1. *For Level 2 findings, if there is desire to continue study treatment:*
    a. *The investigator will evaluate efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number and/or duration of seizures and/or on the impact on daily functioning.*
    b. *The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, topiramate, or stiripentol), alone or in combination, and not maintained the level of seizure control achieved on ZX008.*
2. *If the investigator feels consideration of continued treatment is warranted due to benefit>risk*

[52] Webb RH, et al. Valvular Regurgitation Using Portable Echocardiography in a Healthy Student Population: Implications for Rheumatic Heart Disease Screening. J Am Soc Echocardiogr 2015:28(8);981-988

and the parent/guardian feels strongly that the child be maintained on the study drug when understanding the risks, the parent/guardian must sign a new consent outlining the additional risk and the child should provide assent if possible.

   a. If both of these conditions are not met, the subject is discontinued from treatment.

3. *The investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review.*
4. *The Co-Chairs of the IPCAB are alerted to the request, and jointly prepare an evaluation of the risk and proposed monitoring plan if applicable for submission to the IDMSC.*
5. *IDMSC will review the applications from the Investigator and the IPCAB and unblind the subject treatment if warranted.*
6. *IDMSC makes a determination of appropriate path, including the possible outcomes:*
   a. Discontinue study drug
   b. Increase frequency of ECHO and ECG monitoring
   c. Add additional ECG and/or ECHO measures to be monitored
   d. Reduce the dose of study drug

	VALVULOPATHY	***PULM HYPERTENSION***
Level (3) Secondary Adjudication by CV Ad Board Members; Likely to Recommend Stop Treatment	- *Any first finding of moderate or greater aortic or mitral regurgitation* - *Progression of aortic or mitral regurgitation to moderate or greater* - *Mitral valve gradient (mean) ≥ 4 mm Hg + additional ECHO and/or clinical signs of left heart failure* - *Aortic valve gradient (mean) ≥ 15 mm Hg + additional ECHO and/or clinical signs of Left heart failure* - *Tricuspid valve gradient (mean) ≥ 4 mm Hg + additional ECHO and/or clinical signs of right heart failure* - *Pumonary* [sic] *valve gradient (mean) ≥ 21 mm Hg + additional ECHO and/or clinical signs of right heart failure*	*TR Jet Velocity of 2.9 - 3.4 with any one additional sign:* o *Change in right ventricle/ left ventricle basal diameter ratio > 1.0* o *Right ventricular acceleration time < 100 msec* o *Dilatation of the inferior caval vein (<50% inspiratory decrease) and/or right atrium dilatation* o *Change in the geometry of the interventricular septum in systole (flattening) with LV eccentricity index > 1.1 in systole and/or in diastole* o *Early diastolic pulmonary regurgitation velocity > 2.2 m/sec* o *TAPSE below 18 mm or below Z-score – 2* *OR* - *TR Jet Velocity > 3.4 regardless of other findings*

1. *The investigator will evaluate efficacy to date based on study diaries and consult with the parent/guardian, and determine whether the achieved benefit justifies consideration of continuing treatment by the IDSMC. MINIMAL efficacy criteria for IDSMC consideration:*
   a. Seizures must be more than 75% improved (number of convulsive seizures per 28 days) on treatment over baseline, and improvement must be consistent
   b. The number, type, duration, and distribution of seizures at baseline should be of a severity which justifies the risk of cardiopulmonary complications, considering the subject's age and overall health

   c. *Subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, topiramate, or stiripentol), alone or in combination, and not maintained the level of seizure control achieved on ZX008.*
2. *If the investigator feels consideration of continued treatment is warranted due to benefit>risk and the parent/guardian feels strongly that the child be maintained on the study drug when understanding the risks, the parent/guardian must sign a new consent outlining the additional risk and the child should provide assent if possible.*
   a. *If both of these conditions are not met, the subject is discontinued from treatment.*
3. *The investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review.*
4. *The Co-Chairs of the IPCAB are alerted to the request, and jointly prepare an evaluation of the risk and proposed monitoring plan if applicable for submission to the IDMSC.*
5. *IDMSC will review the applications from the Investigator and the IPCAB and unblind the subject treatment if warranted.*
6. *IDSMC makes a determination of appropriate path, including the possible outcomes:*
   a. *Discontinue study drug*
   b. *Increase frequency of ECHO and ECG monitoring*
   c. *Add additional ECG and/or ECHO measures to be monitored*
   d. *Reduce the dose of study drug*

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

/s/

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06/25/2020 11:57:32 AM

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